

FIG. 3

Residue	Natural Diversity	Diversity<DNA codon>	% good	%covering
L1-28	SNVDGI	SNVDGI <RDT>	100%	94%
L1-29	ISVGN	ISVG <RKT>	100%	86%
L1-29		IV <RTT>	100%	56%
L1-30	SNKGRYTDA	SNKGGRTTDAE E<RVW>	92%	93%
L1-31	SNTRIDKG	SNTRDKGG AA E<RVW>	75%	95%
L1-31		SNTRIIR <ANW>	100%	94%
L1-32	YNWFSDR	YNFSD ATIV<DHT>	55%	88%
L1-32		YFS <THT>	100%	77%
L2-50	GADWKLES	GAWLS V<KBG>	83%	67%
L2-53	SNTKIR	SNT <AVC>	100%	90%
L3-91	YSRAGH	YSA D<KMT>	75%	74%
		YS <TMT>	100%	66%
L3-92	YGNSDLTHI	YNSDTIFAV <DHT>	67%	64%
		YNSDTA <DMC>	83%	62%
L3-93	SNQTHGDR	SNTGDA <RVT>	83%	80%
		SNTDYAFIV <DHT>	44%	76%
L3-94	STWYLFAPVI	STYLFAPVINDH <NHT>	75%	78%
		STYFIN <WHT>	83%	43%
L3-96	LYWFIRP	LYFPHS <YHT>	67%	52%
		LYFIHN <HWT>	67%	58%
		LFI <HTT>	100%	42%
		LLWR <YKG>	100%	47%
		YF <TWT>	100%	29%
H1-28	TS	TSN <AVT>	67%	92%
		TS <WCC>	100%	90%
		T	100%	54%
H1-30	STNRDG	STTNRDGGAAE <RVM>	73%	96%
		STN <AVT>	100%	90%
H1-31	SNGDTRA	SNGGDTTRAEE <RVM>	91%	95%
		SNGDTA <RVT>	100%	83%
		SNGD <RRT>	100%	82%
H1-32	YSNGFA	YSNT <WMY>	75%	81%
H1-33	AYWGSNTNV	AAYWGGSSDCE* <KVK>	75%	87%
		AGSDTNVI <RNT>	87%	58%
		AYSNTN <DMT>	100%	62%
		AYSD <KMT>	100%	56%
		WG <KGG>	100%	30%
H2-50	RYWVGIEASNL	YWWVGELCDF* <KDK>	67%	49%
		RWVGASLMT <DBG>	78%	59%
		RWG <DGG>	100%	35%
		YVIASNDFT <DHT>	67%	45%
H2-52	SYNKIRDT	SYNIDTAFV <DHT>	67%	79%
		SYNNTA <DMT>	83%	77%
H2-53	SDYGHNTW	SDYHNTAP <NMT>	75%	75%
		SDYNTA <DMT>	83%	66%
H2-54	GSDNKFT	SSDKTTAEY* <DMK>	60%	47%
		SDTNAY <DMT>	67%	47%
		GSDN <RRC>	100%	81%
H2-56	STNDYEGA	SSTTNDYEA *<DMK>	90%	90%
		STNDYA <DMT>	100%	86%
H2-58	YNDRSITH	YNDSTA <DMT>	83%	77%
		YND <DAC>	100%	69%

FIG. 4A Oligo

	93	94	95	96	97	98	99	100	100a	100b	100c	101	102	length Diversity	
oligo	S	R	W	G	G	D	G	F	—	A	M	D	Y	11 1.90E+06	
F59	S	R	W	G	DVK	DVK	DVK	DVK	—	A	M	D	Y	11 1.90E+06	
F63	S	R	DVK	DVK	DVK	DVK	DVK	DVK	—	A	M	D	Y	11 6.00E+08	
F64	S	R	DVK	DVK	DVK	DVK	DVK	NNK	—	A	M	D	Y	11 6.00E+07	
F65	S	R	DVK	DVK	DVK	DVK	DVK	DVK	NNK	A	M	D	Y	12 1.10E+09	
F59	S	R	W	G	DVK	DVK	DVK	DVK	—	A	M	D	Y	11 1.90E+06	
F63	S	R	DVK	DVK	DVK	DVK	DVK	DVK	—	A	M	D	Y	11 6.00E+08	
F64	S	R	DVK	DVK	DVK	DVK	DVK	NNK	—	A	M	D	Y	11 6.00E+07	
F65	S	R	DVK	DVK	DVK	DVK	DVK	DVK	NNK	A	M	D	Y	12 1.10E+09	
F66	S	R	NNK	NNK	NNK	NNK	NNK	NNK	—	A	M	D	Y	11 1.10E+09	
F78	S	R	DVK	DVK	DVK	DVK	DVK	—	—	—	F	D	Y	8 1.90E+06	
F165	A	R/K	DVK	DVK	DVK	DVK	DVK	NNK	—	A	M	D	Y	11 1.20E+08	
F166	A	R/K	W	NVT	DVK	DVK	DVK	DVK	—	A	M	D	Y	11 7.50E+06	
F134	A	R/K/T	NVT	NVT	NVT	NVT	NVT	NVT	—	A	M	D	Y	11 2.90E+06	
F136	A	R/K/T	W	NVT	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F137	A	R/K/T	NVT	W	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F138	A	R/K/T	NVT	NVT	W	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F142	A	R/K/T	NVT	NVT	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F155	A	R/K	W	NVT	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F156	A	R/K	NVT	W	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F157	A	R/K	NVT	NVT	W	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F158	A	R/K	NVT	NVT	NVT	W	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F160	A	R/K	NVT	NVT	NVT	NVT	NVT	W	Y	A	M	D	Y	12 2.90E+06	
F160g	A	R/K	NVT	NVT	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.90E+06	
F165	A	R/K	DVK	DVK	DVK	DVK	DVK	NNK	—	A	M	D	Y	11 1.20E+08	
F166	A	R/K	W	NVT	DVK	DVK	DVK	DVK	—	A	M	D	Y	11 7.50E+06	
F163a	A	R/K	DVK	DVK	DVK	DVK	DVK	DVK	—	A	M	D	Y	11 2.70E+08	
F164a	A	R	DVK	DVK	DVK	DVK	DVK	DVK	DVK	A	M	D	Y	12 6.10E+08	
F164b	A	R	DVK	DVK	DVK	DVK	DVK	DVK	DVK	A	M	D	Y	12 3.60E+09	
F165a	A	R	DVK	DVK	DVK	DVK	DVK	DVK	DVK	Y	A	M	D	Y	13 1.10E+10
F165b	A	R	DVK	DVK	DVK	DVK	DVK	DVK	DVK	DSG	A	M	D	Y	13 6.60E+10
F155	A	R/K	W	NVT	NVT	NVT	NVT	NVT	Y	A	M	D	Y	12 2.30E+07	

FIG. 4C

Oligo	93	94	95	96	97	98	99	100	100a	100b	100c	101	102	length	Diversity			
F66c	S	R	W	G	G	D	G	F	-	Y	A	M	D	Y	10	1.00E+08		
F66d	A	R	NNS	NNS	NNS	NNS	NNS	NNS		Y	A/GN	M	D	Y	10	4.00E+08		
F66e	A	R	NNS	NNS	NNS	NNS	NNS	NNS		KSG	A/GN	M	D	Y	9	3.10E+06		
F66f	A	R	NNS	NNS	NNS	NNS	NNS	NNS		Y	A/GN	M	D	Y	9	1.20E+07		
F66a1	A	R	NNS	NNS	NNS	NNS	NNS	NNS		KSG	A/GN	M	D	Y	11	3.20E+09		
F66b1	A	R	NNS	NNS	NNS	NNS	NNS	NNS		Y	A/GN	M	D	Y	11	1.28E+10		
F66g	A	R	NNS	NNS	NNS	NNS	NNS	NNS		KSG	A/GN	M	D	Y	12	1.23E+10		
F66h	A	R	NNS	NNS	NNS	NNS	NNS	NNS		Y	A/GN	M	D	Y	12	3.28E+12		
F66i	A	R	NNS	NNS	NNS	NNS	NNS	NNS		NNS	Y	A/GN	M	D	Y	13	1.31E+13	
F66j	A	R	NNS	NNS	NNS	NNS	NNS	NNS		NNS	KSG	A/GN	M	D	Y	13	1.26E+13	
F171c	A	R/K	NNK	NNK	NNK	NNK	NNK	-	-	-	F	D	Y	Y	8	3.20E+07		
F171d	A	R/K	NNK	NNK	NNK	NNK	NNK	NNK	-	-	F	D	Y	Y	9	1.02E+09		
F171e	A	R/K	NNK	NNK	NNK	NNK	NNK	NNK	-	-	F	D	Y	Y	10	3.28E+10		
F171	A	R/K	NNK	NNK	NNK	NNK	-	-	-	-	F	D	Y	Y	7	1.00E+06		
F185	A	R/K	XYZ	XYZ	XYZ	XYZ					F	D/A	Y	Y	7			
F186	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ			F	D	Y	Y	10			
F187	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ		F	D	Y	Y	11			
F190	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	Y	A	M	D	Y	14		
F190a	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ		Y	A/V/G	M	D	Y	13		
F190b	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ		KSG	A/V/G	M	D	Y	13		
F190c	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	KSG	A/V/G	M	D	Y	14		
F190d	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	Y	A/V/G	M	D	Y	15	
F190e	A	R/K	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	XYZ	KSG	A/V/G	M	D	Y	15	

MRT RHSN KSG WSAG
GBT AVG GNT AVGD

FIG. 5

Light Chain Designed Diversity **Diversity: $\sim 2.9 \times 10^9$**

CDR-L1: diversity $\sim 7 \times 10^3$

28	29	30	31	32
RDT	RTT	RVW	RVW	DHT
D	I	D	D	A
G	V	E	E	D
I		G	G	F
N		K	K	I
S		N	N	N
V		S	S	S
		T	T	T
		R	R	V
				Y

CDR-L2: diversity = 18

50	53
KBG	AVC
A	N
G	S
L	T
S	
V	
W	

CDR-L3: diversity $\sim 2.3 \times 10^4$

91	92	93	94	96
KMT	DHT	DHT	NHT	YHT
A	A	A	A	F
D	D	D	D	H
S	F	F	F	L
Y	I	I	H	P
	N	N	I	S
	S	S	L	Y
	T	T	N	
	V	V	P	
	Y	Y	S	
			T	
			V	
			Y	

FIG. 6

Light Chain Designed Diversity Diversity: $\sim 6.1 \times 10^8$

CDR-L1: diversity $\sim 3.4 \times 10^3$

28	29	30	31	32
RDT	RTT	RVW	ANW	THT
D	I	D	I	F
G	V	E	K	S
I		G	N	Y
N		K	R	
S		N	S	
V		S	T	
		T		
		V		

CDR-L2: diversity = 18

50	53
KBG	AVC
A	N
G	S
L	T
S	
V	
W	

CDR-L3: diversity $\sim 1.0 \times 10^4$

91	92	93	94	96
KMT	DMC	RVT	NHT	YHT
A	A	A	A	F
D	D	D	D	H
S	N	G	F	L
Y	S	N	H	P
	T	S	I	S
	Y	T	L	Y
			N	
			P	
			S	
			T	
			V	
			Y	

FIG. 7

Light Chain Designed Diversity

CDR-L3: diversity $\sim 1.3 \times 10^3$

91	92	93	94	96
TMT	DMC	RVT	WHT	HTT
S	A	A	F	F
Y	D	D	I	I
	N	G	N	L
	S	N	S	
	T	S	T	
	Y	T	Y	

FIG. 8

CDR-L1

28	29	30	31	32
RDT	RTT	RVW	RVW	DHT
D	I	D	D	A
G	V	E	E	D
I		G	G	F
N		K	K	I
S		N	N	N
V		S	S	S
		T	T	T
		V	V	V
				Y

CDR-L2

50	53
DVK	AVM
A	N
G	K
L	R
S	S
V	T2
W	

CDR-L3

91	92	93	94	96
NRT	NRT	RVM	NNK	TDK
C	C	A2	A	C
D	D	D	C	F
G	G	E	D	L
H	H	G2	E	W
N	N	K	F	Y
R	R	N	G	*
S	S	R	H	
Y	Y	S	I	
		T2	L	
			M	
			N	
			P	
			Q	
			R	
			etc	
			*	

*Amber stop codon is encoded by the degenerate codon

FIG. 9

CDR-H1

28	30	31	32	33
WCC	RVM	RVM	WMY	RNT
S	A	A	N	A
T	D	D	S	D
	E	E	T	G
	G	G	Y	I
	K	K		N
	N	N		S
	R	R		T
	S	S		V
	T	T		

CDR-H2

50	52	54	55	57	59
DBG	DHT	NMY	DMT	DMT	DMT
A	A	A	A	A	A
G	D	D	D	D	D
L	F	H	N	N	N
M	I	N	S	S	S
R	N	P	T	T	T
S	S	S	Y	Y	Y
T	T	T			
V	V	Y			
W	Y				

CDR-H3

6-8 "DVK" codons encoding
11 amino acids (ACDEGKNRSYW)

FIG. 10

CDR-H1

28	30	31	32	33
WCC	RVM	RVM	WMY	DMT
S	A	A	N	A
T	D	D	S	D
	E	E	T	N
	G	G	Y	S
	K	K		T
	N	N		Y
	R	R		
	S	S		
	T	T		

CDR-H2

50	52	54	55	57	59
DBG	DMT	DMT	RRC	DMT	DMT
A	A	A	D	A	A
G	D	D	G	D	D
L	N	N	N	N	N
M	S	S	S	S	S
R	T	T		T	T
S	Y	Y		Y	Y
T					
V					
W					

CDR-H3:

6-8 "DVK" codons encoding

11 amino acids (ACDEGKNRSYW) with 18 codons

or 5-8 "NVT" coding 12 amino acids with 12 codons
(SYCPHRTNSADG)

FIG. 11

CDR - H1

28	30	31	32	33
ACC	AVT	RVT	WMY	DMT
T	N	A	N	A
	S	D	S	D
	T	G	T	N
		N	Y	S
		S		T
		T		Y

CDR - H2

50	52	54	55	57	59
DBG	DMT	DMT	RRC	DMT	DAC
A	A	A	D	A	D
G	D	D	G	D	N
L	N	N	N	N	Y
M	S	S	S	S	
R	T	T		T	
S	Y	Y		Y	
T					
V					
W					

CDR - H3

6-8 "DVK" codons encoding

11 amino acids (ACDEG KNRSYW) with 18 codons
or 5-8 "NVT" coding 12 amino acids with 12 codons
(SYCPHRTNSADG)

CDR - L3

91	92	93	94	96
TMT	DMC	RVT	WHT	HTT
S	A	A	F	F
Y	D	D	I	I
	N	G	N	L
	S	N	S	
	T	S	T	
	Y	T	Y	

FIG. 12

CDR-H1

28	30	31	32	33
ACC	AVT	RRT	WMY	DMT
T	N	D	N	A
	S	G	S	D
	T	N	T	N
		S	Y	S
				T
				Y

CDR-H2

50	52	54	55	57	59
DBG	DMT	DMT	RRC	DMT	DAC
A	A	A	D	A	D
G	D	D	G	D	N
L	N	N	N	N	Y
M	S	S	S	S	
R	T	T		T	
S	Y	Y		Y	
T					
V					
W					

CDR-H3

6-8 "NVT" coding 11 amino acids with 12 codons
(SYCPHRTNADG) ($12^6=2.9e6$ - $12^8=4.2e8$)

CDR-L3

91	92	93	94	96
TMT	DMC	RVT	NHT	HTT
S	A	A	A	F
Y	D	D	D	I
	N	G	F	L
	S	N	H	
	T	S	I	
	Y	T	L	
			N	
			P	
			S	
			T	
			V	
			Y	

FIG. 13

CDR-H1

28	30	31	32	33
ACC	AVT	RRT	WMY	KGG/KMT
T	N	D	N	W/A
	S	G	S	G/D
	T	N	T	S
		S	Y	Y

CDR-H2

50	52	54	55	57	59
DGG/DHT	DMT	DMT	RRC	DMT	DAC
R / A	A	A	D	A	D
W /D	D	D	G	D	N
G /F	N	N	N	N	Y
I	S	S	S	S	
N	T	T		T	
S	Y	Y		Y	
T					
Y					

CDR-H3

6 "NVT" coding 11 amino acids with 12 codons
(SYCPHRTNADG) with one W walking through,
or "DVK" (SSYCWTNKSRAADEGG*), * is stop codon

CDR-L3

91	92	93	94	96
TMT	DMC	RVT	NHT	YKG/TWT
S	A	A	A	L2/F
Y	D	D	D	W/Y
	N	G	F	R/
	S	N	H	
	T	S	I	
	Y	T	L	
			N	
			P	
			S	
			T	
			V	
			Y	

FIG. 14A

1 GAAATGAGCT GTTGACAATT AATCATCGGC TCGTATAATG TGTGAAATG TGAGCGGATA ACAATTTCAC ACAGGAAACA GCCAGTCCGT TTAGGTGTTT
CTTTACTCGA CAACTGTTAA TTAGTAGCCG AGCATATTAC ACACCTTAAC ACTCGCCTAT TGTAAAGTG TGTCTTTGT CGGTAGGCA AATCCACAAA
^Ptac promoter

101 TCACGAGCAC TTCACCAACA AGGACCATAG ATTATGAAAA TAAACACAGG TGCACGCATC CTCGCATTAT CCGCATTAAAC GACGATGATG TTTTCGCCT
AGTGCTCGTG AAGTGGTTGT TCCTGGTATC TAATACTTTT ATTTTGTCC ACGTGGGTAG GAGCGTAATA GGCCTAAATG CTGCTACTAC AAAAGGCGGA
^Start male secretion signal

201 CGGCTTATGC ATCCGATATC CAGATGACCC AGTCCCGAG CTCCCTGTCC GCCTCTGTGG GCGATAGGGT CACCATCACC TGCCGTGCCA GTCAGGATGT
GCCGAATACG TAGGCTATAG GTCTACTGGG TCAGGGGCTC GAGGACAGG CCGAGACACC CGTATGCCA GTGCTAGTGG ACGGCACGGT CAGTCTCTACA
^light chain start ^CDR-L1

301 GAATACTGCT GTAGCCTGGT ATCAACAGAA ACCAGGAAAA GCTCCGAAGC TTCTGATTTA CTGGGCATCC TTCTCTACT CTGGAGTCCC TTCTCGCTTC
CTTATGACGA CATCGGACCA TAGTTGCTTT TGGTCTCTTT CGAGGCTTCG AAGACTAAAT GAGCCGTAGG AAGGAGATGA GACCTCAGGG AAGAGCGAAG
^CDR-L2

401 TCTGTAGACC GTTCCGGGAC GGAATTCACCT CTGACCATCA GCAGTCTGCA GCGGGAAGAC TTGCAACTT ATTACTGTCA GCAACATTAT ACTACTCCTC
AGACATCGG CAAGGCCCTG CCTAAAGTGA GACTGGTAGT GGTGACAGT CGSCCTTCTG AAGCTTGAA TAATCACAGT CGTTGTAATA TGATGAGGAG
^CDR-L3

501 CCACGTTCCG ACAGGTACC AAGTGGAGA TCAATCCGA TATCCGATG GCTGATCCGA ACCGTTCCG CGGTAAGAAC CTGGTTTTTC ATTCTGAGAT
GGTGCAAGCC TGTCCCATGG TTCCACCTCT AGTTAGGCT ATACGGCTAC CGACTAGGCT TGGCAAGGC GCCATCTTG GACCAAAAAG TAAGACTCTA
^linker ^gp-tag heavy chain start^

601 CTCCGAGGTT CAGCTGGTGG AGTCTGGCG TGGCTGTGG CAGCCAGGGG GGTCACTCCG TTGTCTCTGT GCAGTTCTG GCTTCAACAT TAAAGACACC
GAGGTCCAA GTCGACCACC TCAGACCCGC ACCGACCAC GTCGTTCCC CGAGTGAGG AAGCAGACA CGTCAAGAC CGAAGTTGA ATTCTGTGG
^CDR-H1

701 TATATACACT GGGTGGCTCA GGCCCGCGGT AAGGCCTGG AATGGTTGC AAGGATTTAT CCTACGAATG GTTATACTAG ATATGCCGAT AGGTCGAAG
ATATATGTA CCCACGAGT CCGGGGCCCA TTCCGGGACC TTACCAACG TTCTTAATA GGATGCTTAC CAATATGATC TATACGGCTA TCGCAGTTCC
^CDR-H2

801 GCCGTTTAC TATAAGGCA GACATATCCA AAAACACAGC CTACCTACAA ATGAACAGCT TAAGAGCTGA GGACACTGCC GTCTATTATT GTAGCCGCTG
CGGCAAGTG ATATTCGGT CTGTGTAGT TTTTGTGTCG GATGATGTT TACTTGCGA ATTCTGACT CCTGTGACG CAGATAATAA CATCGGCGAC
^CDR-H3

901 GGGAGGGGAC GGCTTCTATG CTATGGACTA CTGGGTCAA GGAACACTAG TCACCGTCTC CAGCAGTGGC GGTGGCTCTG GTTCCGGTGA TTTTGATTAT
CCCTCCCTG CGAAGATAC GATACCTGAT GACCCAGTT CCTTGTGATC AGTGGCAGAG GTGCTCACC CCACGAGAC CAAGGCCACT AAAACTAATA
^start p3 C-terminal domain

FIG. 14B

1001 GAAAAGATGG CAAACGCTAA TAAGGGGGCT ATGACCGAAA ATGCCGATGA AAACGGCGTA CAGTCTGACG CTAAGGCCAA ACTTGATTCT GTCGCTACTG
CTTTTCTACC GTTTGCGATT ATTCCCCCGA TACTGGCTTT TACGGCTACT TTGCGCGAT GTCAGACTGC GATTCCGTT TGAACATAAG CAGCGATGAC
1101 ATTACGGTGC TGCTATCGAT GGTTCATTG GTGACGTTTC CGGCCTTGCT AATGTAATG GTGCTACTGG TGATTTTGCT GGCTCTAATT CCCAAATGGC
TAATGCCACG ACGATAGCTA CCAAAGTAAC CACTGCAAG GCCGGAACGA TTACCAATTAC CACGATGACC ACTAAAACGA CCGAGATTAA GGGTTTACCG
1201 TCAAGTCGGT GACGGTGATA ATTACCTTT AATGAATAAT TTCCGTCAAT ATTTACCTTC CCTCCCTCAA TCGGTTGAAT GTCGCCCTTT TGTCTTTAGC
AGTTCAGCCA CTGCCACTAT TAAGTGGAAT TTACTTATTA AAGGCAGTTA TAAATGGAAG GGAGGGAGTT AGCCAACTTA CAGCGGGAAA ACAGAAATCG
1301 GCTGGTAAAC CATATGAATT TTCTATTGAT TGTGACAAAA TAACTTATT CCGTGGTGC TTTCGCTTC TTTTATATGT TGCCACCTTT ATGTATGTAT
CGACCAATTG GTATACTTAA AGATAACTA ACACGTGTTT ATTTGAATTA GGCACCACAG AAACGCCAAG AAATATATAA ACGGTGGAAA TACATACATA
1401 TTCTACGTT TGCTAACATA CTGCGTAATA AGGATCTTAA A
AAAGATGCAA ACGATTGTAT GACGCATTAT TCCTCAGAAAT T
^p3 end

FIG. 15A

1 GAAATGAGCT GTTGACAATT AATCATCGGC TCGTATAATG TGTGAATTG TGAGCGGATA ACAATTTTAC ACAGGAAACA GCCAGTCGGT TTAGGTGTTT
CCTTACTCGA CAACTGTTAA TTAGTAGCCG AGCATATTAC ACACCTTAAC ACTCGCCTAT TGTAAAGTG TGTCTTTGT CGGTACGGCA AATCCACAAA
^ptac promoter

101 TCACGAGCAC TTCACCAACA AGGACCATAG ATTATGAAA TAAACACAGG TGCAAGCATC CTCGATTAT CGCATTTAAC GAGCATGATG TTTTCCGGCT
AGTGCTCGTG AAGTGGTTGT TCCTGGTATC TAATACTTTT ATTTTGTCC AGTGGGTAG GAGCGTAATA GCGGTAAATG CTGCTACTAC AAAAGCGGGA
^Start male secretion signal

201 CGGCTTATGC ATCCGATATC CAGATGACCC AGTCCCGAG CTCCTGTCC GCCTCTGTGG GCGATAGGT CACCATCACC TGCCTGSCCA GTCAGGATGT
GCCGATACG TAGGCTATAG GTCTACTGGG TCAGGGGCTC GAGGGACAGG CGGATATCCA GGTATAGTGG ACGGCACGGT CAGTCCTTACA
^light chain start ^CDR-L1

301 GAATACTGCT GTAGCCTGGT ATCAACAGAA ACCAGGAAA GCTCCGAGC TTCTGATTTA CTGGCATCC TTCTCTACT CTGGAGTCCC TTCTCGCTTC
CTTATGACGA CATCGGACCA TAGTTGTCTT TGGTCTTTT CGAGGCTTCG AAGACTAAAT GAGCGTAGG AAGGATAGA GACCTCAGGG AAGAGCGAAG
^CDR-L2

401 TCTGGTAGCC GTTCCGGGAC GGATTTCACT CTGACCATCA GCACTGTGCA GCGGAGAGC TTGCAACTT ATTACTGTCA GCAACATTAT ACTACTCCTC
AGACCATCGG CAAGGCCCTG CCTAAAGTGA GACTGGTAGT CGTCAGACGT CGCCTTCTG AAGCGTTGAA TAATGACAGT CGTTGTAATA TGATGAGGAG
^CDR-L3

501 CCAGGTTCCG ACAGGTTACC AAGTGGAGA TCAATTCGGA TATGCCGATG GCTGATCGA ACCGTTTCCG CGGTAGAAC CTGGTTTTTC ATTCTGAGAT
GGTGCAAGCC TGTCCCATGG TTCCACCTCT AGTTTAGCCT ATACGGCTAC CGACTAGGCT TGGCAAGGC GCCATTCTTG GACCAAAAAG TAAGACTCTA
^linker ^gd-tag heavy chain start^

601 CTCGAGGTT CAGCTGGTGG AGTCTGGCGG TGGCCTGGTG CAGCCAGGG GCTCACTCCG TTTGTCTCTGT GCAGCTTCTG GCTTCAACAT TAAAGACACC
GAGGCTCCAA GTCGACCACC TCAGACCACC ACCGGACCAC GTCGGTCCCC CGAGTGAGGC AAACAGGACA CGTCGAAGAC CGAAGTTGTA ATTTCTGTGG
^CDR-H1

701 TATATACACT GGTGCGTCA GGCCCGGGT AAGGGCTGG AATGGTTGC AAGGATTTAT CCTAGCAATG GTTATACTAG ATATGCCGAT AGGTCGAAGG
ATATATGTGA CCCACGCAGT CCGGGGCCCA TTCCCGGACC TTCCCTAAATA GGATGCTTAC CAATATGATC TATACGCTA TCGCAGTTCC
^CDR-H2

801 GCCGTTTAC TATAAGCGCA GACACATCCA AAAACACAGC CTACCTACAA ATGAACAGCT TAAGAGCTGA GGACACTGCC GTCTATTATT GTAGCCGCTG
CGGCAAGTG ATATTCCGCT CTGTGTAGT TTTTGTGTG GATGGATGTT TACTTGTCGA ATTCGACT CCTGTGACGG CAGATAATAA CATCGGGAC
^CDR-H3

901 GGGAGGGGAC GGCTTCTATG CTATGGACTA CTGGGTCAA GGAACACTAG TCACCGTCTC CAGCACATGC CCGCGGTGCC CAGCACAGA ACTGCTGGGC
CCCTCCCTG CCGAAGATAC GATACCTGAT GACCCAGTT CCTGTGATC AGTGGCAGAG GTCTGTAGG GCGGACCG GTCTGTGTCT TGAGGACCCG
^start zipper

FIG. 15B

1001 GGCCGCATGA AACAGCTAGA GGACAAGGTC GAAGAGCTAC TCTCCAAGAA CTACACACCTA GAGAATGAAG TGGCAAGACT CAAAAAATT GTCGGGGAGC
CCGGCGTACT TTGTCGATCT CCTGTTCAG CTTCTCGATG AGAGGTCTT GATGGTGAT CTCTTACTTC ACCGTCTGA GTTTTTTGAA CAGCCCTCG
1101 GCGGAAAGCT TAGTGGCGGT GGCTCTGGTT CCGTGTGATT TGATTATGAA AAGATGGCAA ACCTAATAA GGGGGCTATG ACCGAAAATG CCGATGAAAA
CGCCTTTTCA ATCACCAGCA CCGAGACCAA GGCCACTAAA ACTAATACTT TTCTACCGTT TGGGATTATT CCCCCGATAC TGGCTTTTAC GGCTACTTTT
^start p3 C-terminal domain
1201 CGCGCTACAG TCTGACGCTA AAGCAAACCT TGATTCTGTC GCTACTGATT ACGGTGCTGC TATCGATGGT TTCATTGGTG ACGTTTCCGG CCTTGCTAAT
GGCGGATGTC AGACTGGAT TTCCGTTTGA ACTAAGACAG CGATGACTAA TGCCACGACG ATAGCTACCA AAGTAACCCAC TGCAAAGGCC GGAACGATTA
1301 GGTAAATGGT CTAATGGTGA TTTTGCTGGC TCTAATTTCC AAATGGCTCA AGTCGGTGAC GGTGATAATT CACCTTTAAT GAATAATTTC CGTCAATAAT
CCATTACCAC GATGACCACT AAAACGACCG AGATTAAAGG TTACCGAGT TCAGCCCACTG CCACATAATA GTGGAAAATTA CTTATTAAAG GCAGTTATATA
1401 TACCTTCCCT CCTCAATCG GTTGAATGTC GCCCTTTTGT CTTTAGCGCT GGTAAACCAT ATGAATTTTC TATTGATTGT GACAAAATAA ACTTATTCCG
ATGGAAGGGA GGGAGTTAGC CAACTTACAG CGGGAATAACA GAAATCGCGA CCATTTGGTA TACTTAAAAG ATAACATAACA CTGTTTTAAT TGAATAAGGC
1501 TGGTGTCTTT GCGTTTCTTT TATATGTTGC CACCTTTATG TATGTATTTT CTACGTTTGC TAACATACTG CGTAATAAGG AGTCTTAA
ACCACAGAAA CGCAAGAAA ATATACAACG GTGGAATAAC ATACATAAAA GATGCAACG ATTGTATGAC GCAATTATTCC TCAGAAAT
^p3 end

FIG. 16A

1 GAATGAGCT GTTGACAATT AATCATCGGC TCGTAAATG TGTGGAAATG TGAGGGGATA ACAATTTCAC ACAGGAACA GCCAGTCCGT TTAGTGTTT
CTTTACTCGA CAACTGTAA TTAGTAGCG AGCAATATAC ACACCTTAAC ACTCGCTAT TGTAAAGTG TGTCTTTGT CGGTACGGCA AATCCACAAA
*ptac promoter

101 TCACGAGCAC TTCACCAACA AGGACCATAG ATTATGAAA TAAACAAGG TGCACGCATC CTGCAATTAT CCGCAATTAAC GAGATGATG TTTCCGCCT
AGTGCTCGTG AAGTGGTGT TCCTGGTATC TAATACTTTT ATTITGTCC ACGTGGTAG GAGCGTAATA GCGTAATTTG CTGCTACTAC AAAGGCGGA
*Start male secretion signal

201 CGGCTTATGC ATCCGATATC CAGATGACCC AGTCCCGAG CTCCTGTGCC GCCTCTGTGG GCGATAGGGT CACCATCACC TCGGTGCGCA GTCAGGATGT
GCCGATACG TAGGCTATAG GTCTACTGGG TCAGGGGCTC GAGGGACAGG CGGAGACACC CGCTATCCCA GTGGTAGTGG ACGGCACGGT CAGTCTTACA
*light chain start

301 GAATACTGCT GTAGCTGGT ATCAACAGAA ACCAGGAAA GCTCCGAAGC TTCTGANTTA CTCGGCATCC TTCCTCTACT CTGGAGTCCC TTCTCGCTTC
CTTATGACGA CATCGGACCA TAGTTGTCTT TGTCTCTTTT CGAGGCTTCG AAGACTAAAT GAGCCGTAGG AAGGAGATGA GACCTCAGGG AAGAGCGAAG
*CDR-L2

401 TCTGGTAGCC GTTCCGGGAC GGAITTTCACT CTGACCATCA GCATCTGCA GCCGGAAGAC TTGCGCACTT ATTACTGTCA GCAACATTTT ACTACTCTC
AGACCATCGG CAAGGCCCTG CCTAAGTGA GACTGTAGT GGTGAGCTG CGGCTTCTG AAGCGTTGAA TAATGACAGT CGTTGTATAA TGATGAGGAG
*CDR-L3

501 CCAGGTTTCG ACAGGGTACC AAGTGGAGA TCAACGAAC TGTGGCTGCA CCATCTGTCT GCATCTGAT GAGCAGTTGA AATCTGGAAC
GGTGCAAGCC TGTCCCATGG TTCCACCTCT AGTTGTGTG ACACGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTGCTCACT TTAGACCTTG

601 TGCCTCTGTT GTGTGCTGC TGAATAACTT CTATCCAGA GAGGCCAAG TACAGTGGAA GGCCTCCAAT CGGTAACCTC CCAGGAGGT
ACGGAGACAA CACACGGAGC ACTTATTGAA GATAGGCTCT CTCGCTTTC ATGTCACCTT CCACCTATTG CGGGAGGTTA GCCATTGAG GGTCTCTCTCA

701 GTACAGAGC AGGACAGCA GGACAGCAC TACAGCCTCA GCAGCACCTT GAGGCTGAGC AAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCAAG
CAGTGTCTG TCCTGTCTT CCTGTCTGT ATGTCGTGG ATGTCGAGT CGTGTGGGA CTCGACTCG TTTCGTCTGA TGTCTTTGT GTTTTCAGAT CGGACGCTTC

801 TCACCCATCA GGGCTGAGC TCGCCCGTCA CAAAGAGCTT CAACAGGGA GAGTGTGGT CCAGTCCGG TATGGCTGAT CCGAACCGTT TCCGCGGTAA
AGTGGGTAGT CCGGACTCG AGCGGCGAGT GTTTCTCGAA GTTGTCCCT CTCACACCAC GGTGAGGCC ATACCGACTA GGCTTGGCAA AGGCGCAAT

901 GGACCTGGCA TAATCGAGG CTGATCTCT ACGCCGGAG CATCTGGCC CTATAGCGCA AGTTCACGTA AAAGGTTAA CTAGAGTTG AGGTGATTTT
CCTGGACCGT ATTGAGCTCC GACTAGAGA TCGGCGCTGC GTAGCACCG GATCATGGT TCAAGTGCAT TTTTCCCATT GATCTCCAAC TCCACTAAAA
*light chain stop

1001 ATGAAAAGA ATATCGCAT TCTTCTTGA TCTATGTTG TTTTCTAT TGCTACAAC GCGTAGCTG AGATCTCCA GGTTCAGCTG GTGGAGTCTG
TACTTTTCT TATAGCGTAA AGAAGACGT AGATACAGC AAAAAAGATA ACGATGTTG CGCATGCGAC TCTAGAGCT CCAAGTCGAC CACCTCAGAC
*start still secretion signal

*heavy chain start

FIG. 16B

1101 GCGGTGGCT GGTGAGCCA GGGGGCTCAC TCGTTTGTG CTGTGAGCT TCTGGCTTCA ACATTAAAGA CACTATATA CACTGGTGC GTGAGGCCCC
CGCCACCGA CCACGTGGT CCCCAGTG AGGCAACAG GACACGTGA AGACGAGT TGTAAITCT GTGATATAT GTGACCCAG CAGTCCGGG
*CDR-H1

1201 GGGTAAGGC CTGGAATGG TTGCAAGAT TTATCTAG ATGGTTATA CTAGATAGC CGATAGGTC AAGGCCGTT TCACTATAAG CGCAGACACA
CCCATTCCG GACCTTACCC ACGTTCCCTA AATAGATGC TTACCAATAT GATCTATAG GCTATGCGA TTCCGGGCAA AGTGATATTC CGGTCTGTG
*CDR-H2

1301 TCCAAAACA CAGCCTACCT ACAATGAAC AGCTTAAGAG CTGAGGACAC TGCGTCTAT TANTGTAGCC GCTGGGGAGG GGACGGGTTT TATGCTATGG
AGGTTTTGT GTCCGATGA TGTITACTTG TCGAATCTC GACTCTGTG ACGGAGATA ATAACATCG CGACCCCTCC CCTGCCGAAG ATACGATACC
*CDR-H3

1401 ACTACTGGG TCAAGGAACC CTGTACCG TCTCTCGG CTCCACCAAG GGCCTATCG TCTTCCCTT GGCACCTCC TCCAAGACA CCTCTGGGG
TGATGACCC AGTTCTCTGG GACCAGTGG AGAGAGCCG GAGGTGGTTC CCGGTAGCC AGAAGGGGA CCGTGGGAG AGGTCTCTGT GGAGACCCCC

1501 CACAGCGCC CTGGGCTGCC TGGTCAAGGA CTACTTCCC GAACCGTGA CGGTGTCTG GAACTCAGG GCCCTGACCA GCGGCGTGA CACCTTCCG
GTGTGCGCG GACCCGACG ACCAGTTCT GATGAAGGG CTGCGCACT GCCACAGAC CTTGAGTCCG CGGACTGT CGCCGCACGT GTGGAAGGCG

1601 GCTGTCTAC AGTCTCTAG ACTCTACTCC CTCAGCAGG TGGTGACCGT GCCCTCCAG AGCTTGGGA CCCAGACCTA CATCTGCAAC GTGAATCACA
CGACAGATG TCAGGAGTCC TGAGATGAG GAGTCTGCG ACCACTGGA CCGGAGTGG TCGAACCCGT GGTCTGGAT GTAGACGTTG CACTTAGTGT

1701 AGCCAGCAA CACCAAGTC GACAAGAA TTAGGCCAA ATCTTGTAC AAACTCAC CCAGTGGCG TCGGTCTGT TCGGTGAT TTGATTATGA
TCGGTCTGT GTGGTTCCAG CTGTCTTTC AACTCGGT TAGAACACTG TTTGAGTGG AGTCACCGCC ACCGAGACCA AGGCCACTAA AACTAATACT
*start p3 C-terminal domain

1801 AAAGATGCA AACGTAATA AGGGGCTAT GACCGAAAAT GCGATGAAA ACGCGTACA GTCTGAGCT AAAGCAAC TTGATTCTGT CGCTACTGT
TTTCTACCG TTGCGATTAT TCCCCCGATA CTGGCTTTTA CCGCTACTTT TCGCGATGT CAGACTGGA TTTCGTTTG AACTAAGACA GCGATGACTA

1901 TACGGTGTG CTATCGATG TTTCAITGT GACGTTCCG GCCTTGTAA TGGTAATGTT GCTACTGGT ATTTGCTGG CTCTAATCC CAAATGGTC
ATGCCAGAC GATAGCTACC AAGTAACCA CTGCAAGGC CGGAACGAT ACCATTACA CGATGACCAC TAAACGACC GAGATTAAAG GTTTACCGAG

2001 AAGTCGGTA CCGTGATAAT TCACCTTAA TGAATAATT CCGTCAATAT TTACCTTCC TCCTCAATC GGTGAATGT CGCCCTTTTG TCTTTAGCG
TTCAGCACT GCCACTATA AGTGAAAT ACTTATTA GGCAGTTATA AATGGAAGG AGGAGTTAG CCACTTACA GCGGGAAC AGAATCGG

2101 TGGTAAACA TATGAATTT CTATTGATG TGACAAATA AACTTATCC GTGGTCTTT TGGTCTCTT TTATAGTTG CCACCTTAT GTATGTATT
ACCAITTTGT ATACTTAAA GATAACTAAC ACTGTTTTAT TTGAATAGG CACCACAGAA ACCGAAAGAA AATATACAA GGTGGAATA CATACATAA

2201 TCTAGTTTG CTAACATACT GCGTAATAAG GAGCTTAA
AGATGCAAC GATTGTATGA CGCATTAATC CTCAGAAAT
*end p3

FIG. 17A

1 GAAATGAGCT GTTGACAATT AATCATCGGC TGGTATAATG TGTGGAATG TGAGCGGATA ACAATTTAC ACAGGAACA GCCAGTCCGT TTAGGTGTTT
CTTTACTCGA CAACGTGTAA TTAGTAGCG AGCATATTAC ACACCTTAAC ACTCGCTAT TGTAAAGTG TGTCCTTTGT CGGTCAAGCA AATCCACAAA
*ptac promoter

101 TCAGGAGCAC TTCACCAACA AGGACCATAG ATTATGAAAA TAAAAACAGG TGCAGCATC CTGCAATTAT CCGCATTAAC GAGCATGATG TTTTCGCCCT
AGTGCTCGTG AAGTGGTGT TCCTGGTATC TAATACCTTT TAATACCTTT ATTTTGTCC AGTGCGTAG GAGCGTAATA GCGTAATTG CTGCTACTAC AAAGCGGA
*Start male secretion signal

201 CGGCTTATGC ATCCGATATC CAGATGACCC AGTCCCGAG CTCCTGTGCC GCCTCTGTGG GCGATAGGGT CACCATCACC TGCCGTGCCA GTACGATGT
GCCGAATACG TAGCTATAG GTCTACTGG TCAGGGGCTC GAGGACAGG CGGTATCCCA GTGGTAGTGG ACGCACGGT CAGTCTTACA
*light chain start *CDR-L1

301 GAATACGTCT GTAGCTGGT ATCAACAGAA ACCAGGAAAA GCTCGAAGC TTCTGATTTA CTGCGCATCC TTCTCTACT CTGGAGTCCC TTCTCGCTTC
CTTATGACGA CATCGGACCA TAGTTGTCTT TGGTCTTTT CGAGGCTTCG AAGACTAAAT GAGCCGTAGG AAGCATGTA GACCTCAGG AAGAGCGAAG
*CDR-L2

401 TCTGTAGGCC GTTCCGGGAC GGAATTTCACT CTGACCATCA GCAGTCTGCA GCCGGAAGAC TTCCGAACTT ATTACTGTCA GCAACATTAT ACTACTCTTC
AGACCATCGG CAAGGCCCTG CCTAAAGTGA GACTGGTAGT CGTCAGACGT CGGCTTCTG AAGCTTGAA TAATGACAGT CGTTGTAATA TGATGAGGAG
*CDR-L3

501 CCACGTTCCG ACAGGTACC AAGTGGAGA TCAACGAAC TGTGCTGCA CCATCTGTCT TCATCTTCCC GCATCTGAT GAGCAGTTGA AATCTGGAAC
GGTGAAGCC TGTCCCATGG TTCCACCTCT AGTTTGTCTG ACACGACGT GGTAGACAGA AGTAGAAGGG CGGTAGACTA CTCGTCAACT TTAGACCTTG

601 TGCTCTGTT GTGTGCTGC TGAATTAATT CTATCCAGA GAGGCCAAG TACAGTGGAA GGTGGATTAAC GGCCTCCAAT CGGTAACCTC CCAGGAGAGT
ACGGAGACAA CACAGGAGG ACTTATTGAA GATAGGTCT CTCCGGTTTC ATGTCACTT CCACCTATTG GCGGAGTTA GCCCATTGAG GGTCTCTTCA

701 GTACACAGC AGGACAGCAA GGACAGCAC TACAGCCTCA GCAGCACCT GCAGCTGAGC AAAGCAGACT ACGAGAAACA CAAAGTCTAC GCCTGCGAAG
CAGTGTCTCG TCCTGTCTGT CCTGTCTGTG ATGTGGAGT GTGCTGGGA CTGCGACTCG TTTCTCTGA TGTCTTTGT GTTTCAGATG CGGACGCTTC

801 TCACCCATCA GGGCTGAGC TCGCCGCTCA CAAAGAGCTT CAACAGGGA GAGTGTGTTG CCAGTCCGG TATGGTGTAT CCGAACCGTT TCCGCGGTAA
AGTGGGTAGT CCGGACTCG ACGGGCAGT GTTCTCTGAA GTTGTCCCT CTCACACAC GGTGAGGCC ATACCGACTA GGTCTGGCAA AGCGGCCAAT

901 GGACCTGGCA TAATCTGAG CTGATCTCT ACGCGGAGC CATCTGGCC CTAGTAGCCA AGTTCACTGA AAAGGGTAA CTAGAGTTG AGTGATTTT
CCTGGACCGT ATTGAGCTCC GACTAGGAGA TCGCGCTGC GTAGCACCGG GATCATGCGT TCAAGTGAT TTTTCCCAT TATCTCCAAC TCCACTAAAA
*light chain stop

1001 ATGAAAAAGA ATATCGCAT TCTTCTTGCA TCTATGTTG TTTTCTAT TGTACAAC GGTAGGCTG AGATCTCGA GGTTCAGCTG GTGAGTCTG
TACTTTTCT TATAGGTAA AGAAGACGT AGATACAAGC AAAAAAGATA ACGATGTTG CGCATGCGC TCTAGAGCT CCAAGTCGAC CACCTCAGAC
*start stII secretion signal *heavy chain start

FIG. 17B

1101 GCGTGGCCCT GGTGAGCCCA GGGGGCTCAC TCCGTTTGTC CTGTGAGCT TCTGGCTTCA ACATTAAGA CACCTATATA CACTGGGTGC GTACAGGCCCC
GCCACCCGGA CCACGTGGGT CCCCCAGTG AGGCAACAG GACACGTGA [^]CDR-H1 GTGATATAT GTGACCCACG CAGTCCGGGG

1201 GGGTAAGGGC CTGGAATGGG TTGCAAGGAT TTATCTTACG AATGGTTATA CTAGATATGC CGATAGGCTC AAGGCCGTT TCACTATAAG CGCAGACACA
CCCATTTCCCG GACCTTACCC AACGTTCTTA AATAGGATGC TTACCAATAT GATCTATACG GCTATCGGAG TTCCCGGCAA AGTGATATTC GCGTCTGTGT
[^]CDR-H2

1301 TCCAAAAACA CAGCCTACCT ACAATGAAC AGCTTAAGAG CTGAGGACAC TGCCGTTCTAT TATTGTAGCC GCTGGGGAGG GGACGGCTTC TATGCTATGG
AGGTTTTTGT GTCGGATGGA TGTTTACTTG TCGAATTCTC GACTCCTGTG AGGGCAGATA ATACATCGG CGACCCCTCC CCTGCCGAAG ATACGATACC
[^]CDR-H3

1401 ACTACTGGGG TCAAGGAACC CTGGTCACCG TCTCCTCGGC CTCACCAAG GCGCCATCGG TCTTCCCTCC GGCACCTCC TCCAAGAGCA CCTCTGGGG
TGATGACCCC AGTTCTCTTG GACCAGTGCG AGAGGAGCCG GAGGTGGTTC CCGGGTAGCC AGAAGGGGA CCGTGGGAGG AGGTTCTCGT GGAGACCCCC

1501 CACAGCGGCC CTGGGCTGCC TGGTCAAGGA CTACTTCCCC GAACGGTGA CCGTGTCTGT GAACTCAGC GGCCTGACCA GCGGCGTGCA CACCTTCCCG
GTGTCGCCCG GACCCGAGCG ACCAGTTCTT GATGAAGGGG CTTGGCCACT GCCACAGCAC CTTGAGTCCG CCGGACTGGT CGCCGCACT GTGGAAGGGC

1601 GCTGTCTTAC AGTCTCAGG ACTCTACTCC CTCAGCAGCG TGGTGACCTT GCGCTCCAGC AGCTTGGGA CCCAGACCTA CATCTGCAAC GTGAATCACA
CGACAGGATG TCAGGAGTCC TGAGATGAGG GAGTCGTGCG ACCACTGGCA CCGGAGGTGCG TCGRACCCGT GCGTCTGGAT GTAGACGTTG CACTTAGTGT

1701 AGCCCCAGCA CACCAAGTC GACAGAAAG TTGAGCCAA ATCTTGTCAC AAACTCACA CATGCCCGCC GTGCCAGCA CCAGAACTGC TGGGCGGCCG
GTGGGTGCTT GTGGTCCAG CTGTTCTTTC AACTCGGTT TAGAACATG TTTTGAGTGT GTACGGGCGG CACGGGTGCT GGTCTTGACG ACCCGCCCG
[^]start zipper

1801 CATGAACAG CTAGAGGACA AGGTGAAGA GCTACTCTCC AAGAACTACC ACCTAGAA TGAAGTGGCA AGACTCAAA AACTGTGTCG GGAGCGCGGA
GTACTTTGTC GATCTCTGT TCCAGCTTCT CGATGAGG TTCITGATGG TGGATCTCTT ACTTCACCGT TCTGAGTTTT TTGAACAGCC CCTCGCGCCT

1901 AAGCTTAGTG GCGGTGGCTC TGGTTCGGT GATTTGANT ATGAAGAAT GGCAACGCT AATAAGGGG CTATGACCGA AATGCCGAT GAAAACGCGC
TTCGAATCAC CGCCACCGAG ACCAAGCCA CTAAACTAA TACTTTTCTA CCGTTTGGGA TTATTTCCCG GATACTGGCT TTTACGGCTA CTTTGGCGG
[^]start p3 C-terminal domain

2001 TACAGTCTGA CGCTAAAGC AAACITGANT CTGTGCTAC TGATTACGGT GCTGCTATCG ATGGTTTCAT TGGTGAGGTT TCCGGCCTTG CTAATGGTAA
ATGTCAGACT GCGATTTCCG TTGAACTAA GACAGCATG ACTAATGCCA CGAGGATAGC TACCAAAGTA ACCACTGCAA AGCGCGAAC GATTACCAT

2101 TGGTGCTACT GGTGATTTTG CTGGCTCTAA TTCCCAAATG GCTCAAGTC GTGACGGTGA TAAITCACCT TTAATGAATA ATTTCCGTCA ATATTACCT
ACCAAGATGA CCACTAAAAAC GACCGAGAT AAGGGTTTAC CGAGTTTACG CACTGCCACT ATTAAGTGA AATTACTTAT TAAAGGCAGT TATAAATGGA

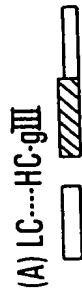
2201 TCCCTCCCTC AATCGTTGA ATGTGCGCCT TTTGTCTTAA GCGCTGGTAA ACCATATGAA TTTTCTATTG ATTGTAGCAA AATAAACTTA TTCGTGGTG
AGGAGGGGAG TTAGCCAAT TACAGCGGA AACAGAAAT CCGGACCAIT TGGTATACTT AAAAGATAAC TAACACTGTT TTATTTGAAT AAGGCACCAC

2301 TCTTTGCGTT TCTTTTATAT GTTGCCACCT TTATGTATGT ATTTCTACG TTTGCTAACA TACTGGTAA TAAGGAGTCT TAA
AGAAACGCAA AGAAAATATA CAACGGTGA AATACATACA TAAAGATGC AAACGATTGT ATGACGCAIT ATTCTCTAGA ATT
[^]end p3

Fig. 18

F(ab) OR F(ab)' 2-PHAGE

(A) LC---HC-gIII



(B) LC---HCZIP(AMBER)-gIII



(C) LC---HCZIP-gIII

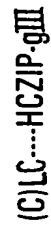
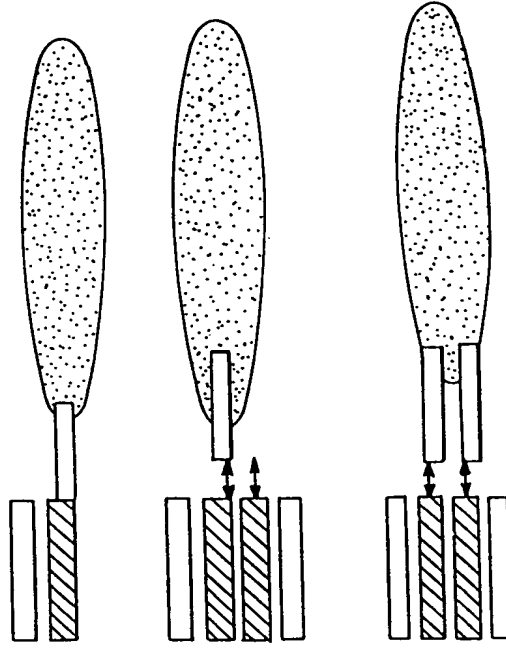



Fig.19

IN SOLUTION BINDING ASSAY, ZIPPED (Fab')₂ PHAGE
BINDS WITH SIMILAR AFFINITY AS Fab-PHAGE

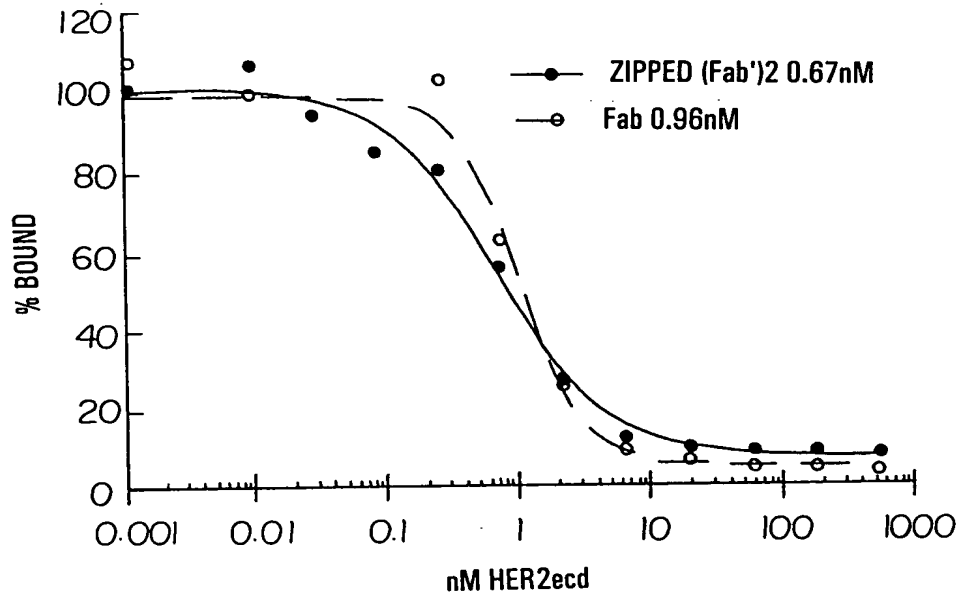


Fig.20

**SLOW OFF-RATE OF ZIPPED Fab
INDICATES THE FORMATION OF (Fab')₂ ON PHAGE**

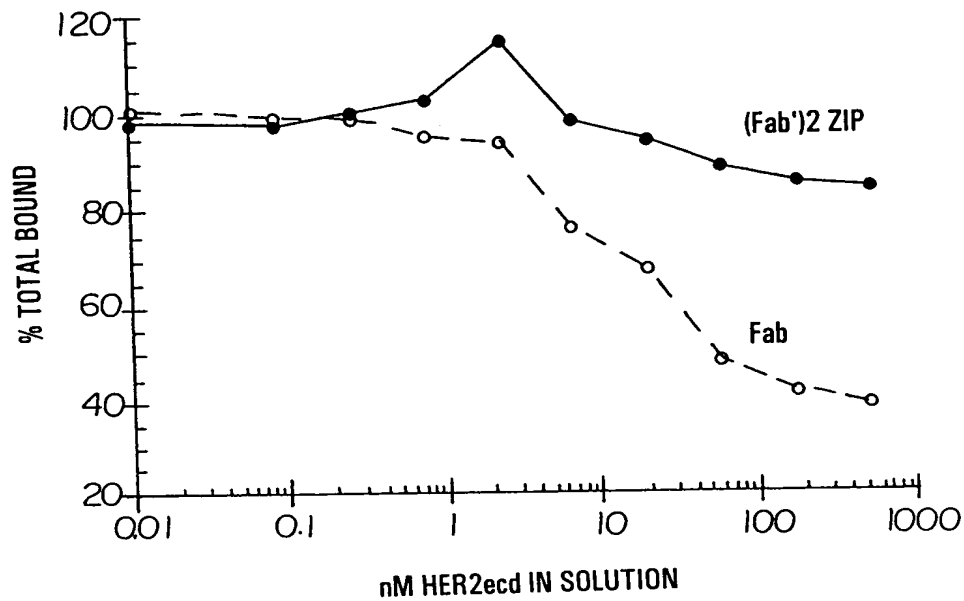


Fig.21

HERCEPTIN WT (0.2nM) BINDING TO HER2ecd

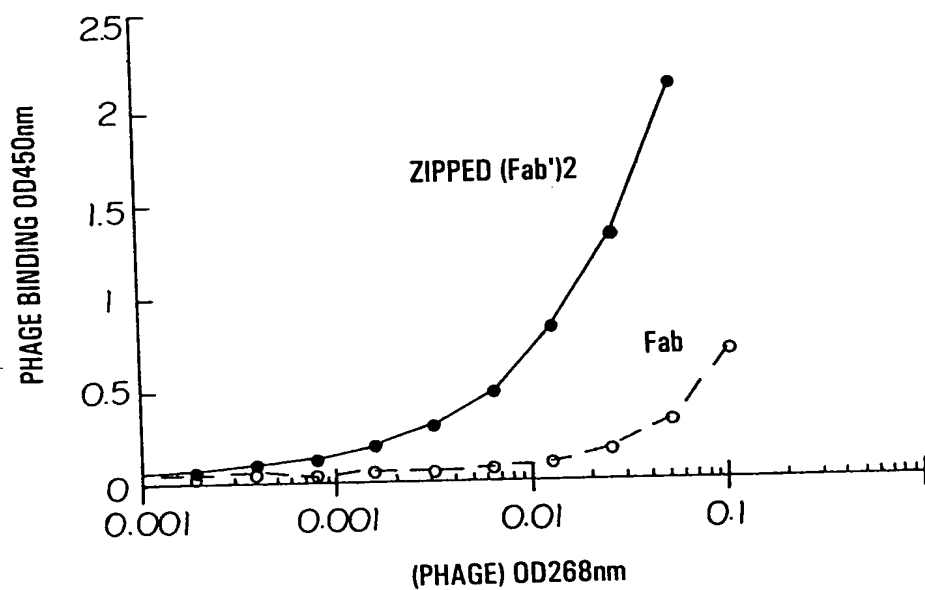


Fig.22

HERCEPTIN (HC/R50A,610nM)
BINDING TO HER2ecd

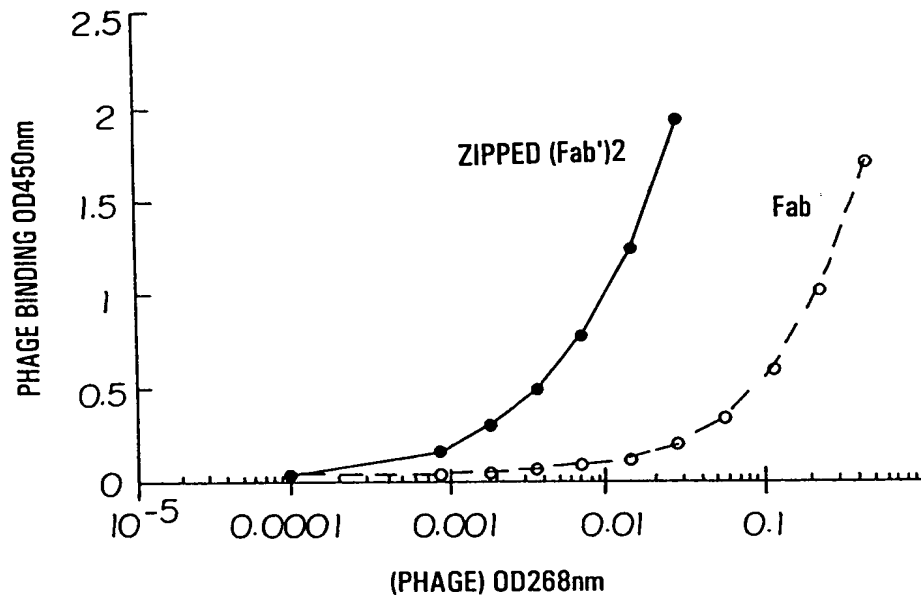
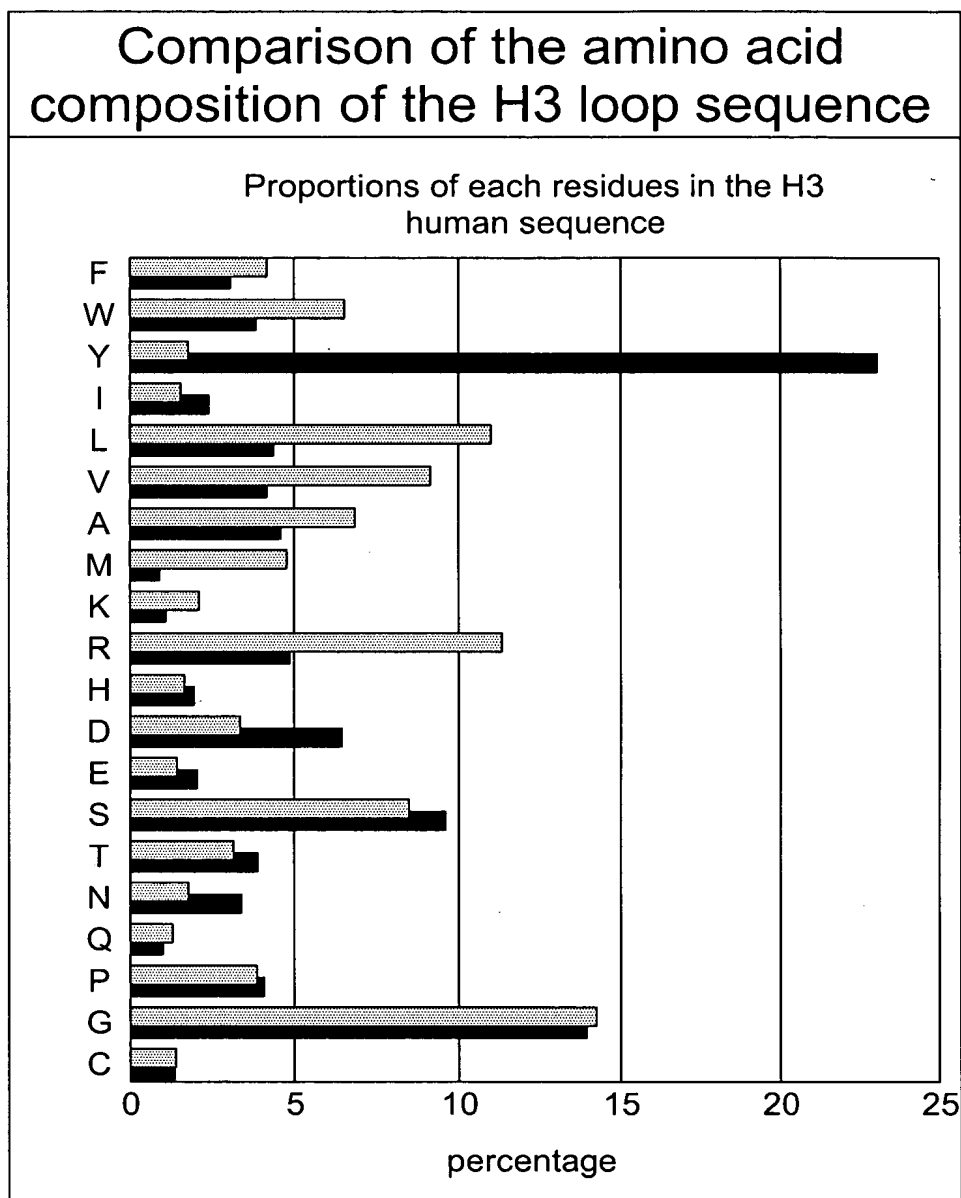


FIG.23



Aliphatic hydrophobic residues occur more frequently in NNK synthetic library than in natural sequences.

FIG. 24

CDR-H1:

28	30	31	32	33
AVT	RVM	RVM	WMY	KVK
N	A2	A2	N	A2
S	D	D	S	C
T	E	E	T	D
	G2	G2	Y	E
	K	K		G2
	N	N		S2
	R	R		Y
	S	S		W
	T2	T2		*

CDR-H2:

50	52	53	54	56	58
KDK	DMT	NMY	DMK	DMK	DMT
C	A	A	A2	A2	A
D	D	D	D	D	D
E	N	H	E	E	N
F	S	N	K	K	S
G2	T	P	N	N	T
L	Y	S	S2	S2	Y
V2		T	T2	T2	
W		Y	Y	Y	
Y			*	*	
*					

*Amber (TAG) stop codon is encoded by the degenerate codon

CDR-H3:

6-8 "DVK" codons (18) encoding
12 amino acids (ACDEGKNRSTYW) and stop (*)

FIG. 25
ScFv Library Sorting Results

Library	Binders		
	Her2	IGF	VEGF
scFv-1 (H1/H2/H3)Zip	100%	100%	63%
ScFv-2 (L3 /H1/H2/H3)Zip	50%	63%	25%
scFv-3 (L3/H3)Zip	88%	88%	88%
scFv-4 (H1/H2/H3)	38%	50%	63%
scFv-5 (L3 /H1/H2/H3)	25%	13%	25%

FIG. 26
Detailed Analysis of scFv Zipper Libraries

Binding clones

Library	IGF		VEGF	
	Total	Specific	Total	Specific
scFv-1	91%	67%	79%	70%
scFv-2	84%	54%	52%	22%
scFv-3	88%	8%	91%	4%

FIG. 27 **Summary of Sequencing Results**

Library	Round	Sequences	
		Total	Unique
anti-IGF			
scFv-1	2	72	65
scFv-1	3	95	79
scFv-4	3	88	48
Sum		255	192
anti-VEGF			
scFv-1	2	24	22
scFv-1	3	87	45
scFv-4	3	91	19
Sum		202	86

FIG. 28

Table X
CDR-H3 Usage in Binding Clones

	95	96	97	98	99	100	100a
4D5	W	G	G	D	G	F	Y
F59	W	G	X	X	X	X	X
F63	X	X	X	X	X	X	X
F64	X	X	X	X	X	X	Y
F65	X	X	X	X	X	X	Y

Percentage of each CDR-H3 in binders

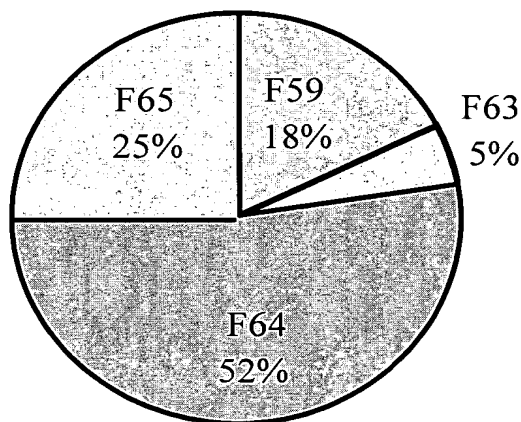


FIG. 29
Binders from L3/H3 library, sort 2
(1-4% hit rate)

H3 Sequences of IGF1 binders (3/8)				
	Sequences	# clones	Source Oligo	IC50 (uM)
I1	<u>SR</u> WKYATR <u>YAM</u>	1	(DVK)5(NNK)1	40
I2	<u>SR</u> SRGWWT <u>AAM</u>	1	(DVK)7	0.3
I3	<u>SR</u> ASRDWYG <u>AM</u>	1	(DVK)7	15
H3 sequences of mVEGF binders (10/25)				
V1	<u>SR</u> NAWA <u>F</u>	6	(DVK)5	5.0
V2	<u>SR</u> NLSNS <u>YAM</u>	1	(NNK)6	0.2
V5	<u>SR</u> AGWAGW <u>YAM</u>	1	(DVK)5(NNK)1	0.6
V8	<u>SR</u> AAKAGW <u>YAM</u>	1	(DVK)5(NNK)1	4.7
V10	<u>SR</u> SDGRDSA <u>YAM</u>	1	(DVK)6(NNK)1	6.0

Fig.30

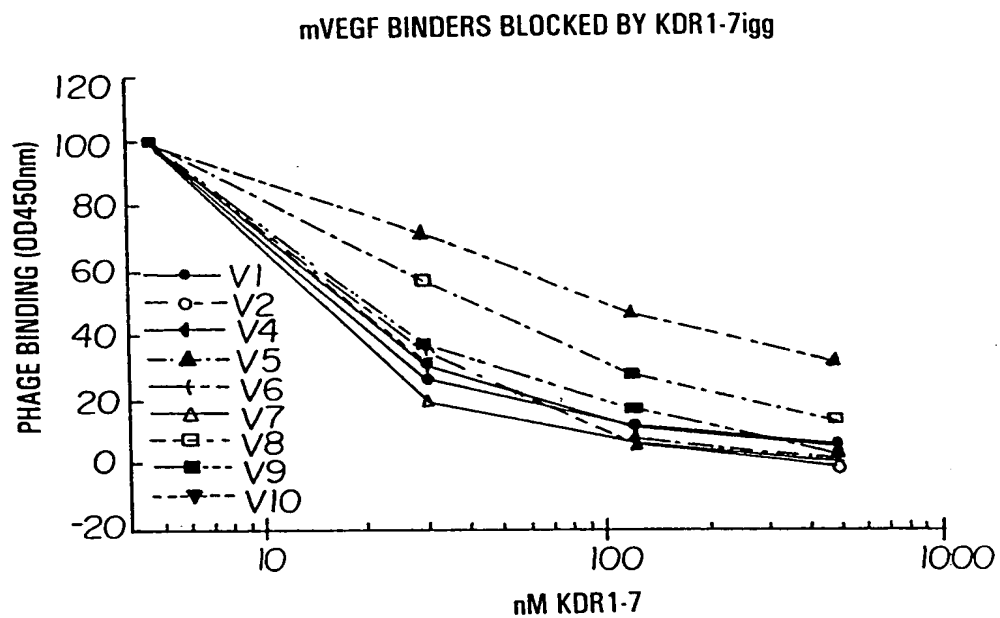


Fig.31

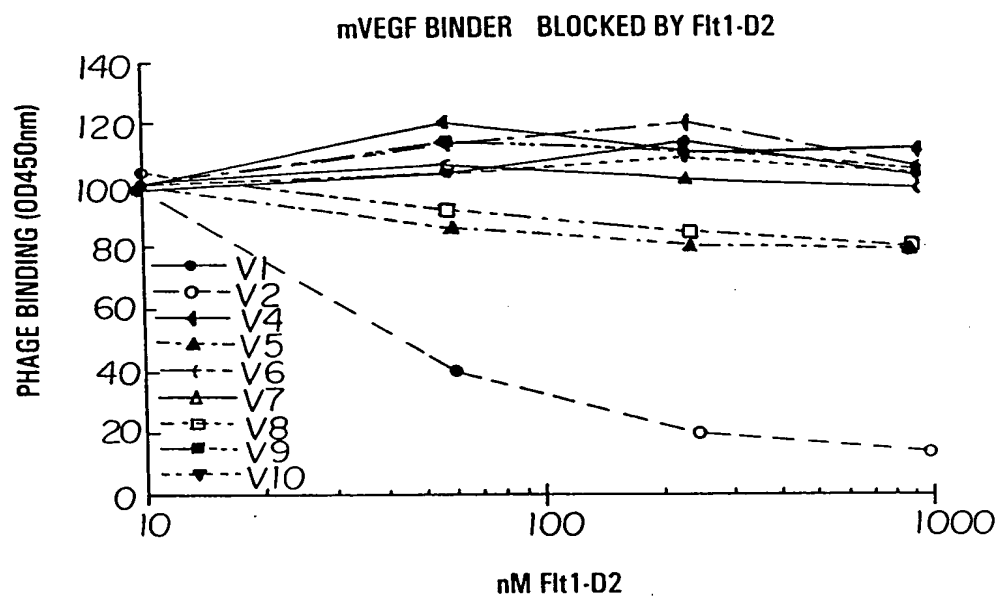


FIG. 32

Further Characterization of the mVEGF binders

	H3 seq	IC50 (uM)	Blocking reagent		Fab Protein
			Flt-D2	Y317	
V1	SRNAWA F	5.0	-	+	-
V2	SR NLSNS YAM	0.2	+	+	+
V5	SR AGWAW YAM	0.6	-	+/-	+
V8	SR AAKAGW YAM	4.7	-	+/-	+

FIG. 33

mVEGF-201	28	30	31	32	33	49	50	52	53	54	56	58	71	93	94	95	96	97	98	99	100	100a	Affinity
	T	T	S	N	G	A	Y	S	S	N	Y	Y	R	A	R	W	S	R	A	S	F	Y	>5uM
	T	T	G	T	D	A	I	T	Y	D	S	Y	R	A	K	A	G	D	R	E	G	Y	200nM
	T	T	D	S	G	G	R	S	Y	S	S	N	R	A	K	W	P	W	Y	N	A	W	700nM
hFc-10	28	30	31	32	33	49	50	52	53	54	56	58	71	93	94	95	96	97	98	99	100	100a	Affinity
	T	N	N	Y	W	G	Y	S	S	Y	G	T	R	A	K	A	X	K	G	S	L	Y	2uM
	T	T	G	N	A																	>1uM	
	T	N	D	Y	Y																		
hFc-11	T	N	D	Y	Y																		
hFc-12	T	N	D	Y	Y																		
hFc-13	T	S	N	T	G																		
hFc-14	T	T	S	Y	G	A	S	S	S	Y	S	Y	R	A	K	Y	X	A	R	E	G	X	
hFc-15	T	N	N	N	S	G	Y	N	S	S	G	S	R	A	K	W	R	T	S	W	K	Y	
hFc-16	T	S	S	S	A	A	W	S	S	N	G	S	R	A	X	T	A	G	G	A	K	Y	
hFc-17	T	T	N	T	W	G	D	Y	Y	D	G	Y	R	A	X	W	R	W	W	G	R	Y	
hFc-18	T	N	G	N	Y	G	W	S	S	N	G	Y	R	A	R	Y	S	G	G	R	R	Y	
hFc-19	T	S	N	N	A	G	R	S	S	Y	N	Y	R	A	X	G	X	T	S	G	G	Y	
hFc-20	T	T	S	N	D	A	W	S	S	Y	N	Y	R	A	R	R	S	R	W	S	R	A	
hFc2	(sequence not determined)																						~2uM

(sequence not determined)

FIG. 34A **Phagemid construct**

A. Vector for Fab-pIII display

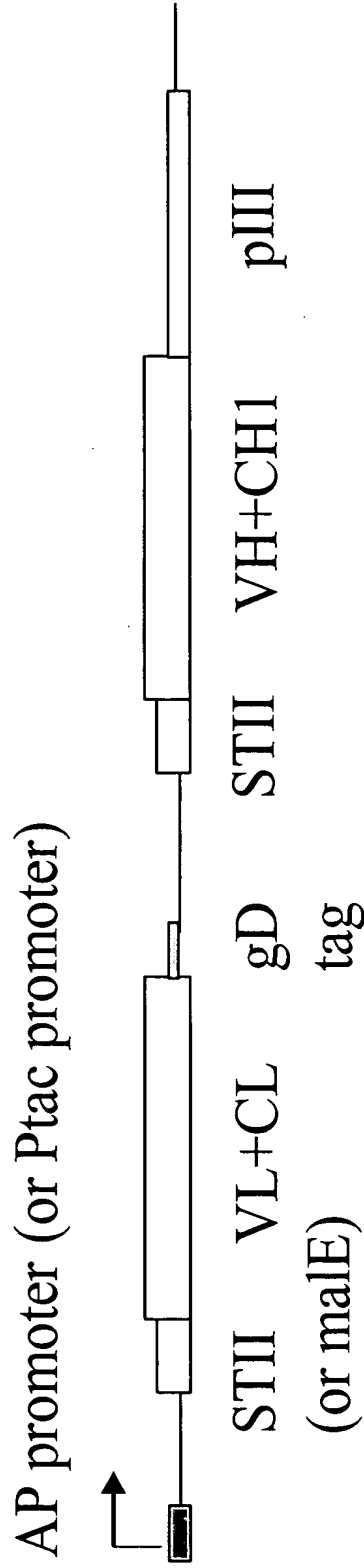


FIG. 34B **Vector for Fab'2-pIII display**

B. Vector for Fab'2-pIII display

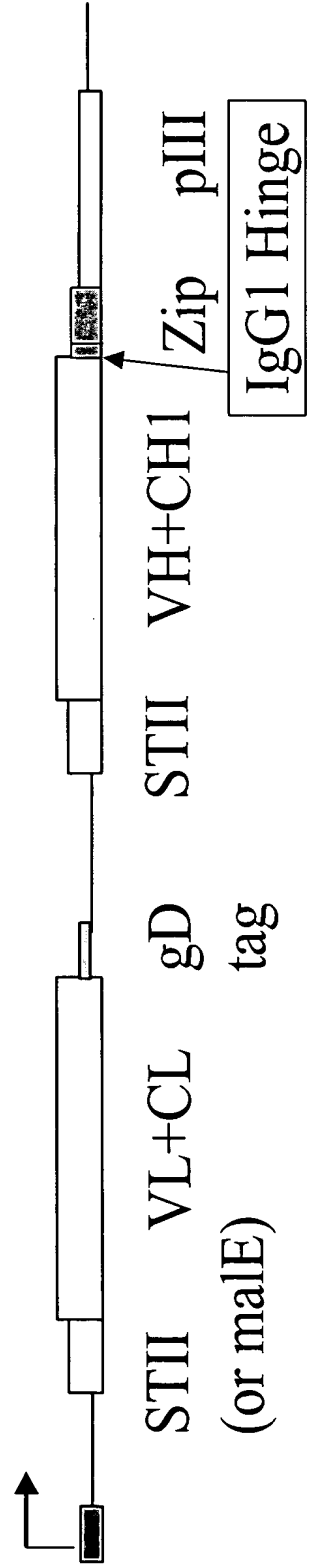


FIG. 34C

C. Vector for $\text{ScF}_V\text{-pIII}$
AP promoter (or Ptac promoter)

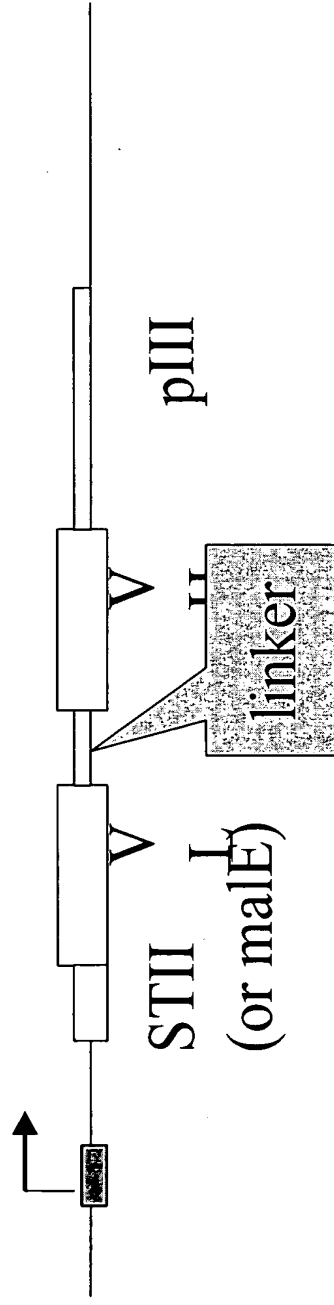


FIG. 34D

D. Vector for $(\text{ScF}_V)_2\text{-pIII}$
AP promoter (or Ptac promoter)

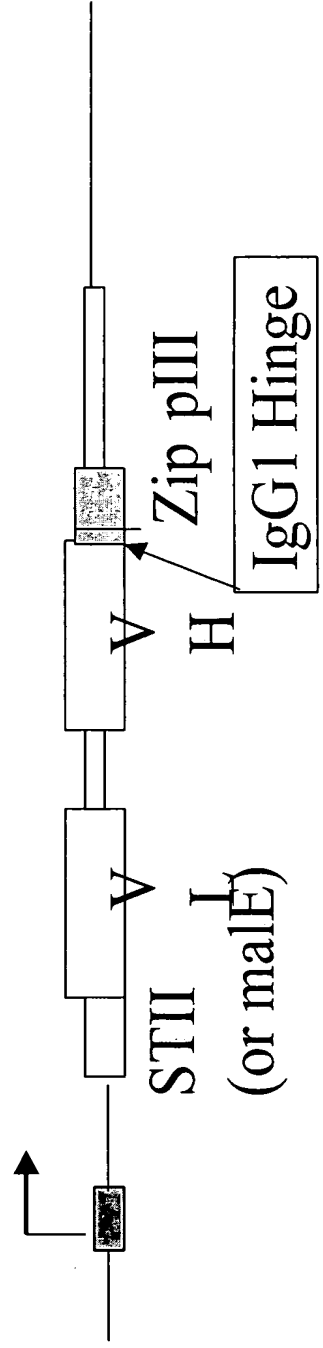


FIG. 35

	28	30	31	32	33	50	52	53	54	56	58	95	96	97	98	99	100	100a	Affinity uM
mVEGF-109	T	G	N	S	W	V	A	T	Y	Y	N	W	G	A	K	G	T	W	0.13
mVEGF-126	N	A	D	S	A	Y	A	Y	D	Y	Y	W	G	W	T	T	N	G	0.58
mVEGF-127	N	D	N	T	A	V	S	H	D	T	Y	W	G	W	E	T	D	G	0.83
mVEGF-130	N	A	D	S	A	L	D	S	S	Y	D	S	R	A	G	Y	T	Y	0.2
mVEGF-136	N	G	K	S	S	W	S	Y	E	A	A	T	S	W	S	K	P	Y	0.45
mVEGF-169	N	T	A	Y	G	V	T	Y	D	D	T	W	G	W	E	A	N	W	0.15
mVEGF-173	T	G	G	S	W	V	Y	T	Y	Y	D	W	G	A	G	G	T	W	0.27
mVEGF-174	T	G	G	S	W	V	S	D	Y	Y	D	W	G	S	G	Y	T	W	0.13
mVEGF-176	S	A	G	Y	D	L	A	Y	A	Y	N	A	A	A	W	A	S	Y	0.7
mVEGF-179	T	T	E	S	G	V	Y	H	D	K	Y	W	W	Y	S	W	N	W	0.13

FIG. 36

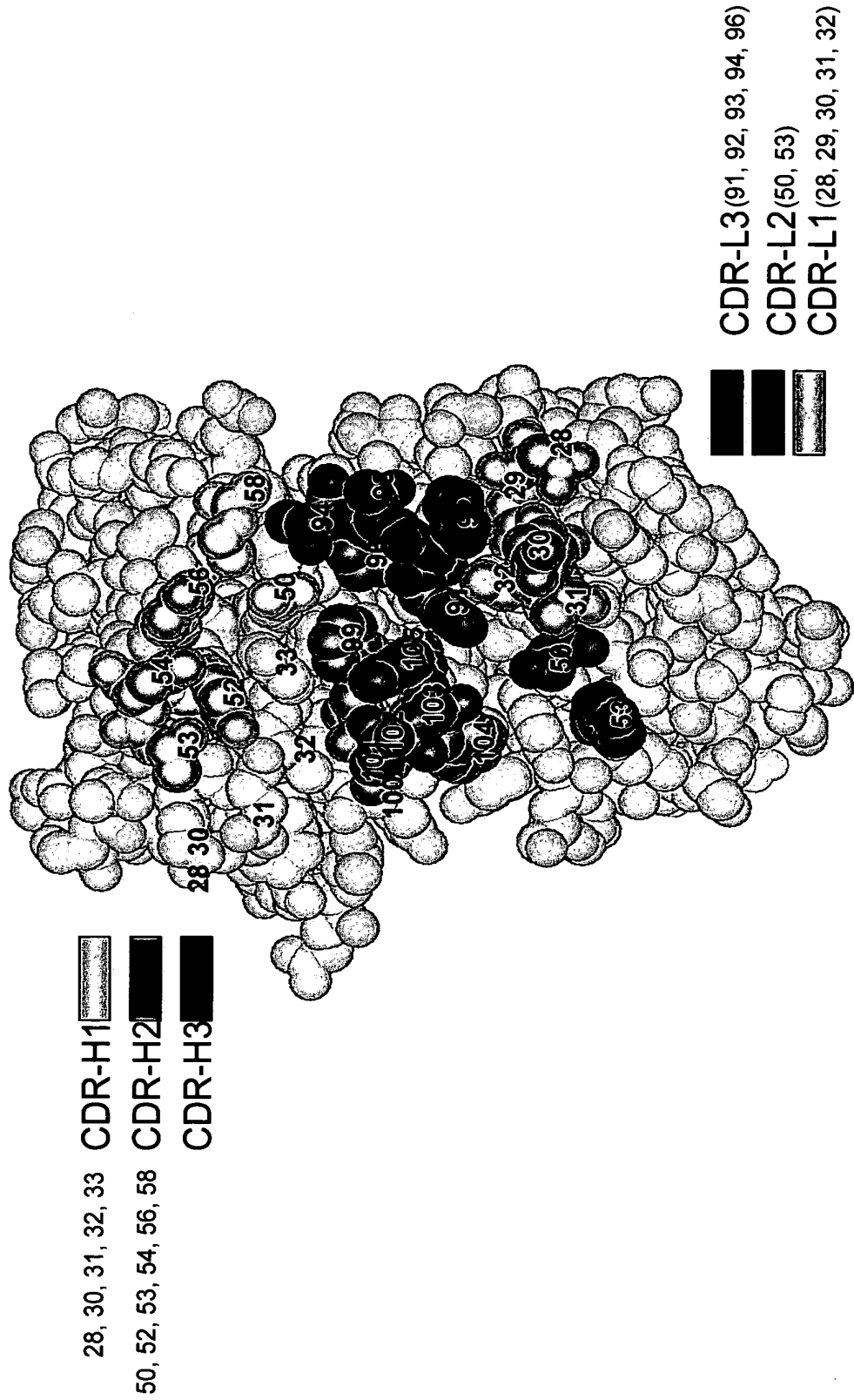


FIG.37

```

GAT GTT CAG TTG CAG GAA TCA GGC GGT GGC TTG GTA CAG GCC GGA 45
GGT TCG TTG CGT TTG TOC TGT GCT GCC TCG GGT OGT ACT GGT TCT 90
ACT TAT GAT ATG GGC TGG TTT CGT CAG GCT OCG GGT AAA GAA CGT 135
GAA TCG GTT GGC GCC ATT AAC TGG GAT TCG GCT OGT ACT TAC TAT 180
GCT TCG TCC GTC OGT GGT CGT TTT ACT ATT TCA OGT GAT AAT GGC 225
AAA AAA ACT GTC TAT TTG CAG ATG AAT TCA TTG AAA CCA GAA GAT 270
ACT GCC GTC TAT ACT TGT GGT GCT GGT GAA GGC GGT ACT TGG GAT 315
TCT TGG GGT CAG GGT ACC CAG GTC ACT GTC TOC TCT GCC GGT GGT 360
ATG GAT TAT AAA GAT GAT GAT GAT AAA TGA 390

```

a.)

```

DVQLQ ESGGG LVQAG GSLRL SCAAS GRTGS TYDMG WFRQA PGKER ESVAE
      5      10      15      20      25      30      35      40      45      50

```

```

INWDS ARTYY ASSVR GRFTI SRDNA KKTVE LQMNS LKPED TAVYT CGAGE
      54      59      64      69      74      79      82b     86      91      96

```

```

GGTWD SWGQG TQVTV SSAGG MDYKD DDDK
      101      106      111      116      121      126

```

b.)

```

C G A G X X X X X X X X X X X X X X X X W G
92 93 94 95 96 97 98 99 100 100a 100b 100c 100d 100e 100f 100g 100h 100i 100j 101 102 103 104

```

c.)

Nucleotide (a.) and amino acid sequence (b.) of the Llama anti-HCG parent scaffold. The numbering system for the 17 Residue CDR3 loop is shown in (c.)

Wild Type CDR3 Alanine Scan

FIG.38

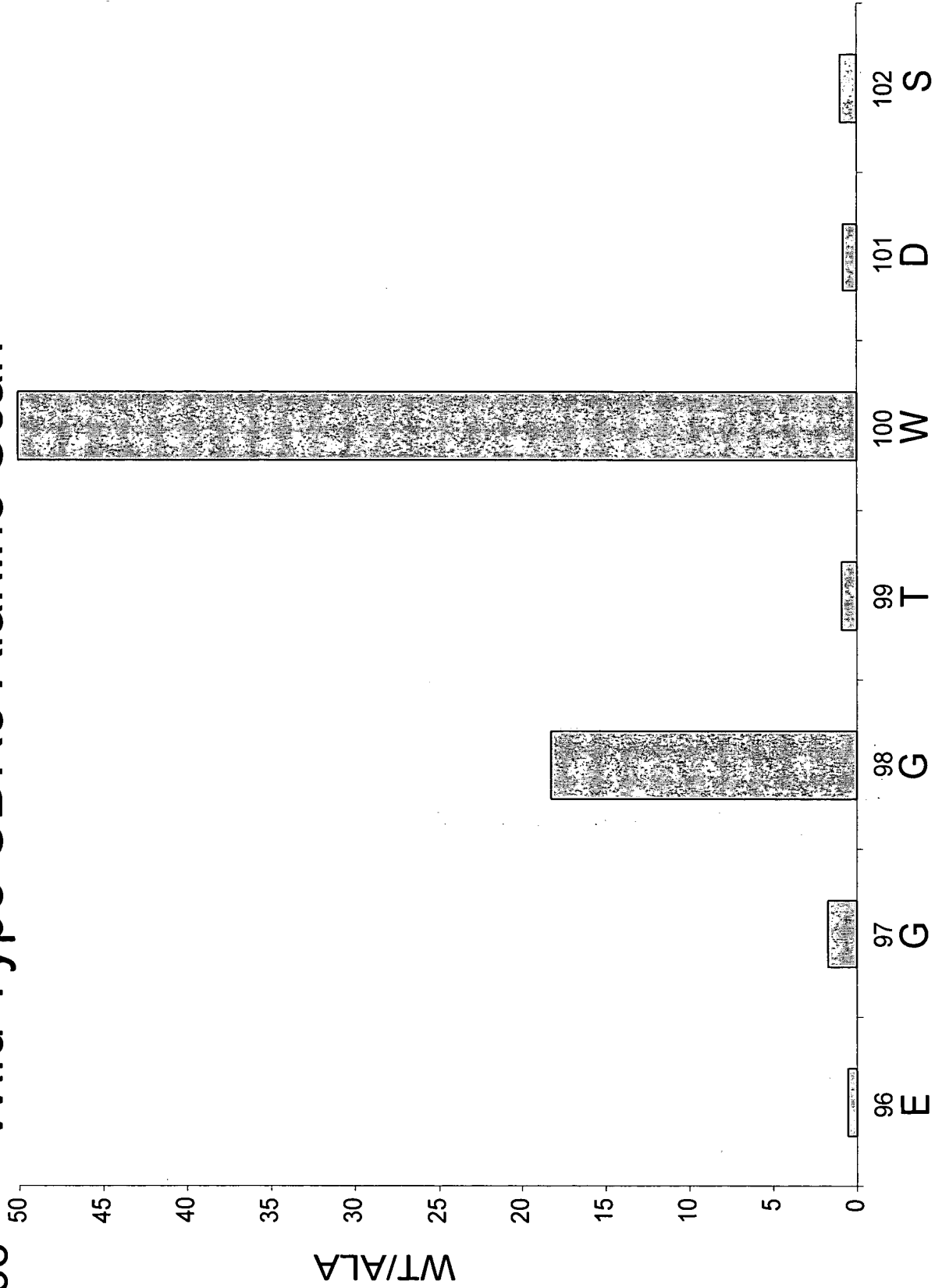
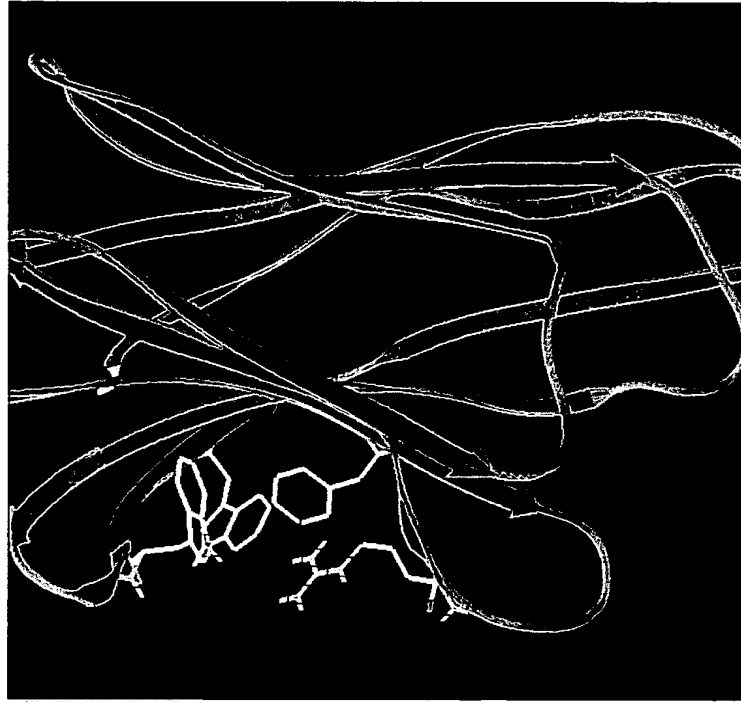
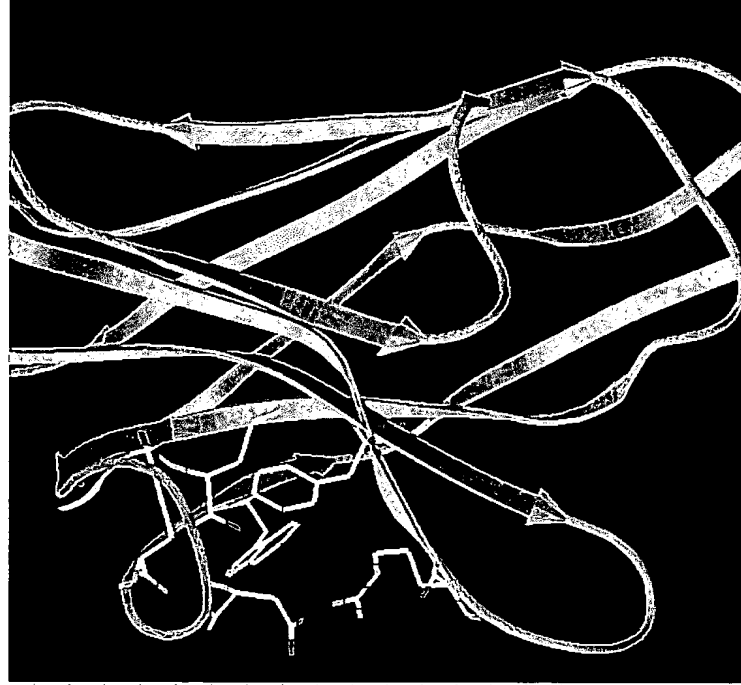


FIG. 39

Interface Packing by CDR3



α -HCG



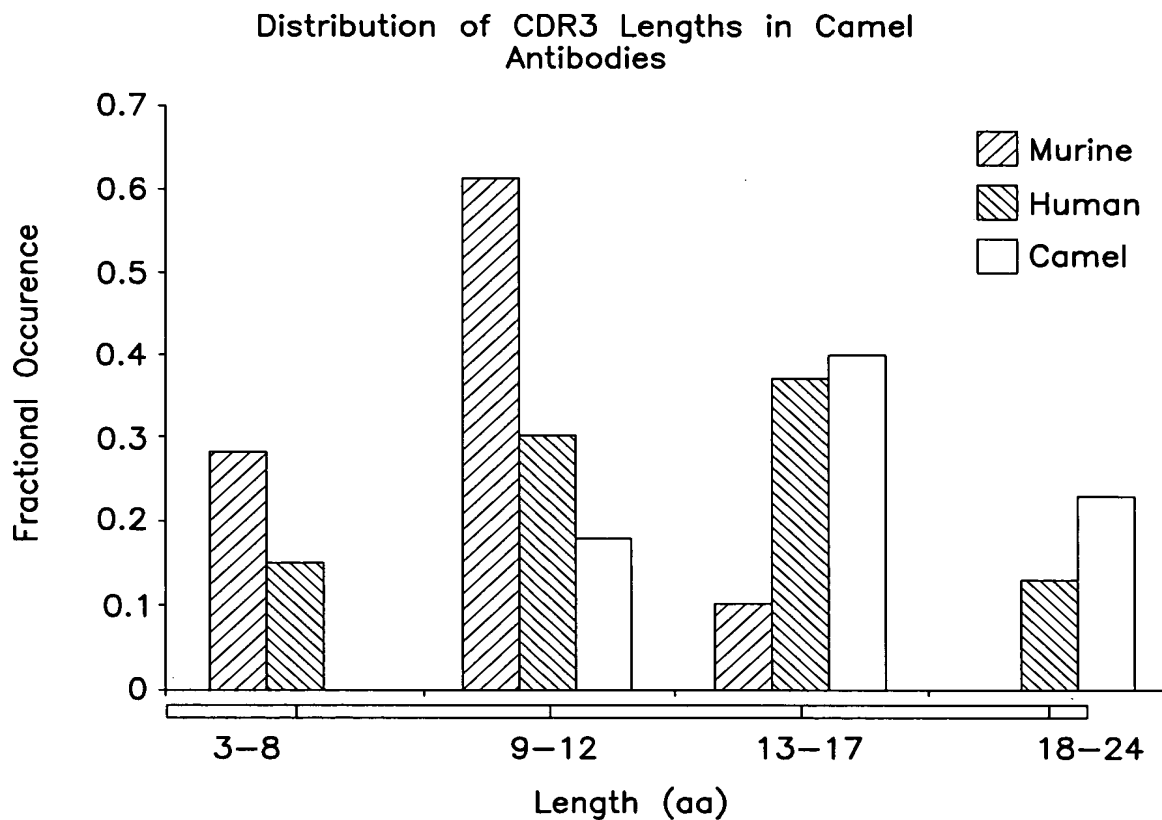
α -RNase A

FIG.40

Amino Acid Bias in VhH Framework

Residue	WT	Codon	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H
37	Phe	NNS		2.8	2.1	0.4			65.8	1.4	21		0.7	0.4					1.4	1.4	0.9	
45	Arg	NNS		1.4	4.4	7.9		4.4		2.9	2.9	8.9	2.9	2.9	1.4		2.9			2.9	47.5	5.9
47	Ser	NNS		6.7	1.1	6.7	2.2	1.1	6.7		29.2	4.4		22.4	3.3		4.4	4.4	4.4		2.2	
91	Thr	NNS		1.9	5.7	14.1	3.8		40.5	9.6	5.7	3.8	0.9	1.2	1.9			3.8		1.9	4.5	

FIG.41



CDR3 in dromedary ad's is longer reflecting dual role

FIG.42 Amino Acid Bias in CDR3

Position	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
96	2	3	1	5	29	1	10	7	13	18	5		3	6	35	6	6	16	11	11
97	3	6			19	6	1	28		52	19		2		8	4	1	15	12	6
98	10	2	3	14	15	15	1	7	15	13	15	3	3	8	20	12	7	14	19	1
99	9	1	7	9	12	13	1	2	10	7	9	11	10	7	32	8	4	8	19	10
100	12	2	16	3	13	24	4	6	7	6	7	3	12	4	18	18	5	8	17	3
100a	8	2	6	10	11	25	2	6	2	10	6	1	12	7	17	10	3	21	26	6
100b	9	4	4	5	26	27	5	6	5	8	1	19	8	4	9	16	5	10	31	4
100c	13	2	5	4	18	33	4	4	11	8	5	17	8	14	10	12	3	4	35	3
100d	11	1	3	12	11	29	5	3	9	18	6	4	6	7	12	8	11	7	25	3
100e	12	3	5	11	15	17	4	2	4	12	6	8	17	6	13	9	5	15	25	5
100f	11	3	8	8	14	12	4	8	3	10	7	13	11	4	16	8	3	15	41	5
100g	10		6	22	35	13	4	2	5	9	13	3	8	2	12	5	11	10	49	4
100h	4	1	4	17	56	9	5	3	3	17	8	1	7	2	9	13	7	3	39	6
100i	9	4	3	7	4	12	3	5	17	8	20	4	5	11	19	10	8	9	40	10
100j	10	2	2	7	8	8		12		13	5	2	27	7	4	7	6	40	23	
101	10	2	2	8	6	6	8	3	11	18	17		3	17	8	8	13	24	31	6
102	22	2	2	2	21	10	3	27	4	4	7	2		9	5	16	6	26	28	14

FIG.43

a

Residue	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H	Total	Frequency
96	2	2	14	16	6	3	23	10	11	5	1	5	5	0	5	1	4	12	32	10	166	0.05
97	4	3	13	47	25	2	16	5	10	17	6	3	1	0	0	0	0	0	7	1	159	0.05
98	1	10	13	10	6	3	14	1	18	14	14	10	5	3	7	3	13	15	18	1	177	0.05
99	1	9	8	7	2	9	12	8	13	9	11	7	3	11	6	6	8	10	30	1	170	0.05
100	2	12	6	6	6	11	13	3	14	7	21	16	5	2	4	14	3	7	15	4	169	0.05
100a	1	7	19	9	6	10	10	4	24	5	23	10	3	1	7	6	8	1	16	1	168	0.05
100b	4	9	10	7	6	6	23	4	29	0	23	15	5	16	3	3	4	5	9	5	184	0.05
100c	2	12	2	7	3	8	17	3	32	4	29	10	3	16	14	4	4	11	9	3	192	0.06
100d	0	10	7	16	3	5	10	3	23	6	27	6	11	4	7	2	12	9	11	5	174	0.05
100e	3	10	14	10	2	15	15	4	23	6	16	8	5	8	3	4	11	4	13	4	177	0.05
100f	2	10	14	10	8	11	12	5	38	7	10	7	2	12	2	7	8	3	15	4	187	0.06
100g	0	9	9	7	2	8	33	3	47	12	12	4	11	3	2	6	20	4	10	4	206	0.06
100h	0	4	3	16	3	6	51	6	35	8	9	13	7	1	1	3	15	3	8	5	195	0.06
100i	4	9	7	8	4	4	4	10	36	19	11	10	8	3	10	2	7	15	17	3	190	0.06
100j	2	8	37	11	12	25	7	0	23	5	7	7	5	2	7	2	7	0	4	0	171	0.05
101	2	8	24	16	3	3	6	6	27	16	5	7	12	0	14	1	7	11	8	8	183	0.05
102	2	21	23	4	26	0	20	13	28	7	10	14	5	2	7	1	2	4	5	3	195	0.06
Total	32	149	220	204	123	125	286	88	431	147	230	153	92	84	99	65	133	114	228	62	3360	
Frequency	0.01	0.04	0.07	0.06	0.04	0.04	0.09	0.03	0.13	0.04	0.07	0.05	0.03	0.03	0.03	0.02	0.04	0.03	0.07	0.02		

b

Residue	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H
96	0.3	-2.0	1.0	1.9	0.0	-1.5	-1.5	2.4	2.7	-2.2	-0.8	-3.2	0.0	-2.0	0.0	-1.2	-1.0	2.7	6.3	4.0
97	2.0	-1.5	0.8	1.0	8.0	-1.6	0.7	0.4	-2.3	3.3	-1.6	-1.7	-1.8	-2.0	-2.2	-1.8	-2.5	-2.3	-1.1	-1.1
98	-0.5	0.6	0.3	-0.3	-0.2	-1.6	-0.3	-1.7	-1.0	2.2	0.4	0.8	0.1	-0.7	0.8	-0.2	2.3	3.7	1.8	-1.3
99	-0.5	0.4	-1.1	-1.2	-1.7	1.1	-0.6	1.7	-1.9	0.6	-0.2	-0.1	-0.8	3.3	0.4	1.5	0.5	1.8	5.4	-1.2
100	0.3	1.5	-1.7	-1.5	-0.1	1.7	-0.4	-0.7	-1.7	-0.1	2.6	3.1	0.2	-1.1	-0.4	5.9	-1.4	0.5	1.1	0.5
100a	-0.5	-0.3	2.3	-0.4	-0.1	1.3	-1.1	-0.2	-0.5	-0.9	3.2	0.7	-0.7	-1.6	-1.0	0.9	1.5	0.5	-2.0	1.2
100b	1.7	0.1	-0.6	-1.4	-0.3	-0.3	1.8	-0.4	1.1	-2.8	2.9	2.2	-0.2	5.9	-1.0	-0.3	-1.2	-0.5	-1.0	0.9
100c	0.1	1.2	-3.0	-1.4	-1.5	0.1	0.2	-0.9	1.5	-1.5	4.2	0.5	-1.2	5.1	3.5	0.2	-1.3	1.8	-1.1	-0.3
100d	-1.3	0.6	-1.4	1.6	-1.3	-0.6	-1.3	-0.7	0.1	-0.6	4.2	-0.7	2.6	-0.2	0.8	-0.7	1.9	1.3	-0.4	1.0
100e	1.0	0.8	0.7	-0.3	-1.8	3.1	0.0	-0.3	0.1	-0.6	1.1	0.0	0.1	1.7	-1.0	0.3	1.5	-0.8	0.2	0.4
100f	0.2	0.6	0.5	-0.4	0.4	1.6	-1.0	0.1	2.9	-0.4	-0.9	-0.5	-1.4	3.4	-1.5	1.8	0.2	-1.3	0.7	0.3
100g	-1.4	0.0	-1.2	-1.5	-2.0	0.0	3.7	0.0	4.0	1.0	-0.6	-1.7	2.1	-0.9	-1.6	1.0	4.2	-1.1	-1.0	0.1
100h	-1.4	-1.6	-2.9	1.1	-1.6	-0.5	8.4	0.4	2.0	-0.2	-1.3	1.4	0.5	-1.8	-2.0	-0.4	2.6	-1.4	-1.4	0.7
100i	1.6	0.0	-1.5	-1.1	-1.1	-1.1	-3.0	2.3	2.4	3.7	-0.5	0.3	1.0	-0.8	1.9	-0.9	-0.2	3.4	1.2	-0.3
100j	0.3	0.0	7.7	0.2	2.3	7.2	-2.0	-2.1	0.2	-0.9	-1.4	-0.2	0.2	-1.1	0.9	-0.7	0.1	-2.4	-2.1	-1.8
101	0.2	0.0	3.3	1.5	-1.4	-1.6	-2.4	0.5	0.7	2.8	-2.1	-0.4	3.1	-2.1	3.7	-1.4	-0.1	1.9	-1.3	2.5
102	0.1	4.1	2.9	-2.4	7.1	-2.7	0.8	3.5	0.6	-0.5	-1.0	1.7	-0.3	-1.3	0.5	-1.4	-2.1	-1.0	-2.4	-0.3

FIG.44

Amino Acid Bias by Residue Type

Residue	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	Y
96	0.01	0.08	0.01	0.03	0.09	0.00	0.16	0.05	0.11	0.08	0.03		0.02	0.05	0.14	0.04	0.06	0.06	0.02	0.11
97	0.02	0.15			0.06	0.02	0.02	0.21		0.23	0.12		0.01		0.03	0.02	0.01	0.06	0.03	0.06
98	0.06	0.05	0.04	0.10	0.05	0.06	0.02	0.05	0.13	0.06	0.10		0.02	0.07	0.08	0.07	0.07	0.06	0.04	0.01
99	0.05	0.03	0.09	0.06	0.04	0.05	0.02	0.02	0.08	0.03	0.06	0.12	0.07	0.06	0.13	0.05	0.04	0.03	0.04	0.10
100	0.07	0.05	0.21	0.02	0.04	0.09	0.06	0.05	0.06	0.02	0.04	0.03	0.08	0.03	0.07	0.11	0.05	0.03	0.04	0.03
100a	0.05	0.05	0.08	0.07	0.04	0.10	0.03	0.05	0.02	0.04	0.04	0.01	0.08	0.06	0.07	0.06	0.03	0.09	0.06	0.06
100b	0.06	0.10	0.05	0.03	0.08	0.10	0.08	0.05	0.04	0.03	0.01	0.21	0.05	0.03	0.04	0.10	0.05	0.04	0.07	0.04
100c	0.08	0.05	0.06	0.03	0.06	0.13	0.06	0.03	0.09	0.03	0.03	0.19	0.06	0.12	0.04	0.07	0.03	0.01	0.07	0.03
100d	0.07	0.03	0.04	0.08	0.04	0.11	0.08	0.02	0.08	0.08	0.04	0.04	0.04	0.06	0.05	0.04	0.11	0.03	0.05	0.03
100e	0.07	0.08	0.06	0.08	0.05	0.07	0.06	0.02	0.03	0.05	0.04	0.09	0.12	0.05	0.05	0.05	0.05	0.06	0.05	0.05
100f	0.07	0.08	0.10	0.06	0.04	0.04	0.06	0.06	0.03	0.04	0.04	0.14	0.08	0.03	0.07	0.04	0.03	0.06	0.09	0.05
100g	0.06		0.08	0.15	0.11	0.05	0.06	0.02	0.04	0.04	0.08	0.03	0.06	0.02	0.05	0.03	0.11	0.04	0.10	0.04
100h	0.02	0.03	0.05	0.12	0.18	0.04	0.08	0.02	0.03	0.08	0.05	0.01	0.05	0.02	0.04	0.08	0.07	0.01	0.08	0.06
100i	0.05	0.10	0.04	0.05	0.01	0.05	0.05	0.04	0.14	0.03	0.13	0.04	0.03	0.10	0.08	0.06	0.08	0.04	0.08	0.10
100j	0.06	0.05	0.03	0.05	0.03	0.03	0.13	0.09		0.06	0.03	0.02	0.19	0.06	0.02	0.04	0.06	0.16	0.05	
101	0.06	0.05	0.03	0.06	0.02	0.02	0.13	0.02	0.09	0.08	0.11		0.02	0.15	0.03	0.05	0.13	0.10	0.07	0.06
102	0.13	0.05	0.03	0.01	0.07	0.04	0.05	0.21	0.03	0.02	0.04	0.02		0.08	0.02	0.09	0.06	0.11	0.06	0.14

Standard Deviations above Average




 > 2
 > 1.5
 > 1

FIG.45a

Percent Abundance Round 3 Round 4	CDR3 Sequence																
	96	97	98	99	100	100a	100b	100c	100d	100e	100f	100g	100h	100i	100j	101	102
3.9	R	I	G	R	S	V	F	N	L	R	R	E	S	W	V	T	W
10.5	L	L	R	R	G	V	N	A	T	P	N	W	E	G	L	V	G
3.3	V	L	R	R	R	V	N	S	V	A	I	F	T	R	V	Q	S
8.3	R	L	K	R	G	G	S	S	V	V	S	W	E	M	P	L	A
6	F	L	V	N	P	L	S	G	L	V	S	T	P	S	G	V	A
4.1	V	V	A	G	R	W	W	W	R	W	R	T	P	M	S	L	A
3.8	V	L	E	L	R	S	S	G	G	N	A	R	W	M	S	L	Y
2.2	L	R	I	S	P	Y	A	F	W	L	G	T	W	A	P	S	Y
1.9	L	W	T	R	A	R	S	W	R	W	W	R	R	R	E	Q	F
1.3	W	R	S	W	I	S	S	I	L	G	L	R	T	W	W	Y	A
1.3	K	S	T	R	W	R	A	G	H	G	R	T	E	H	W	L	S

FIG. 45b

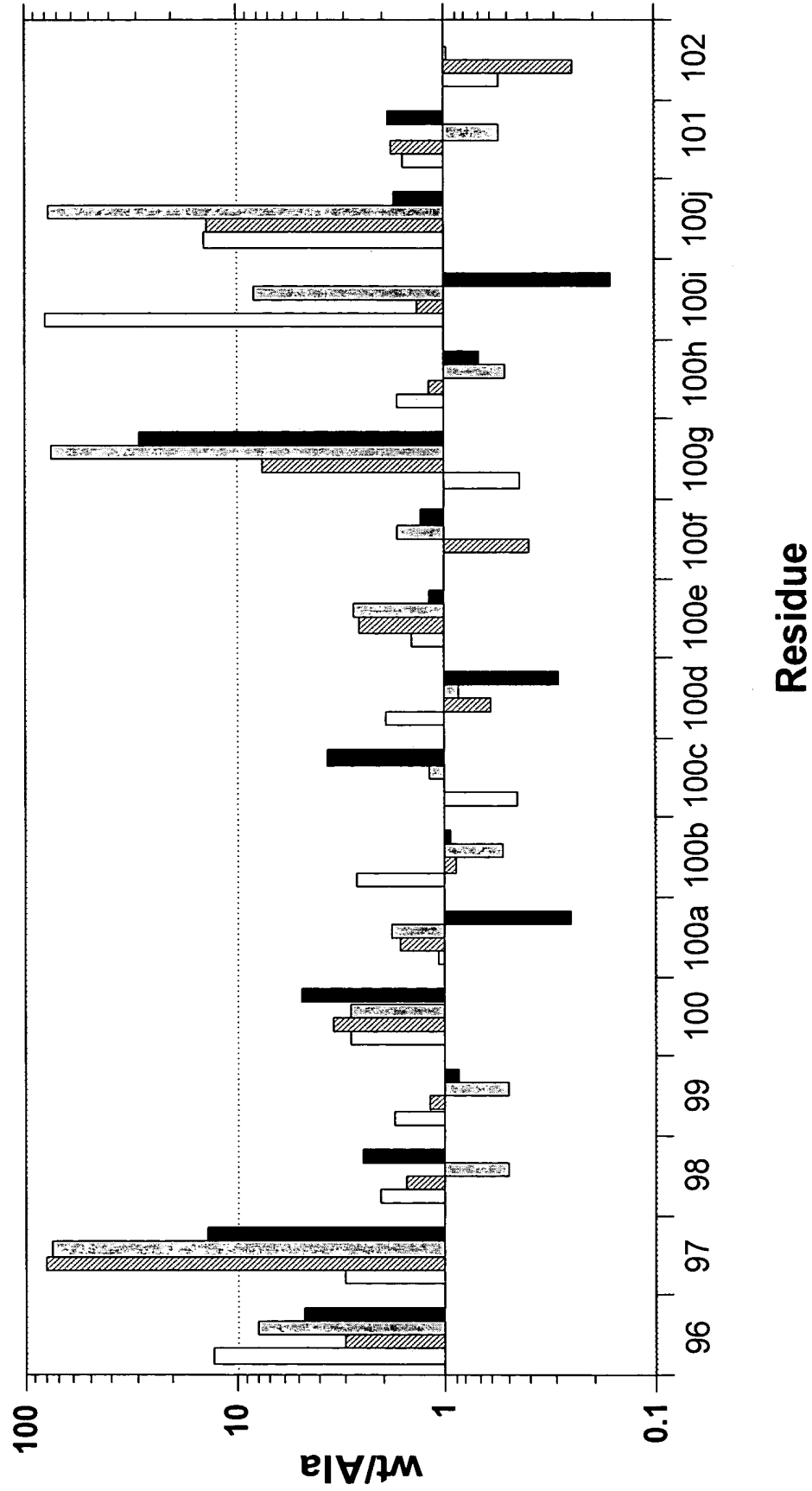


FIG.46 **Distribution of Loop Lengths**

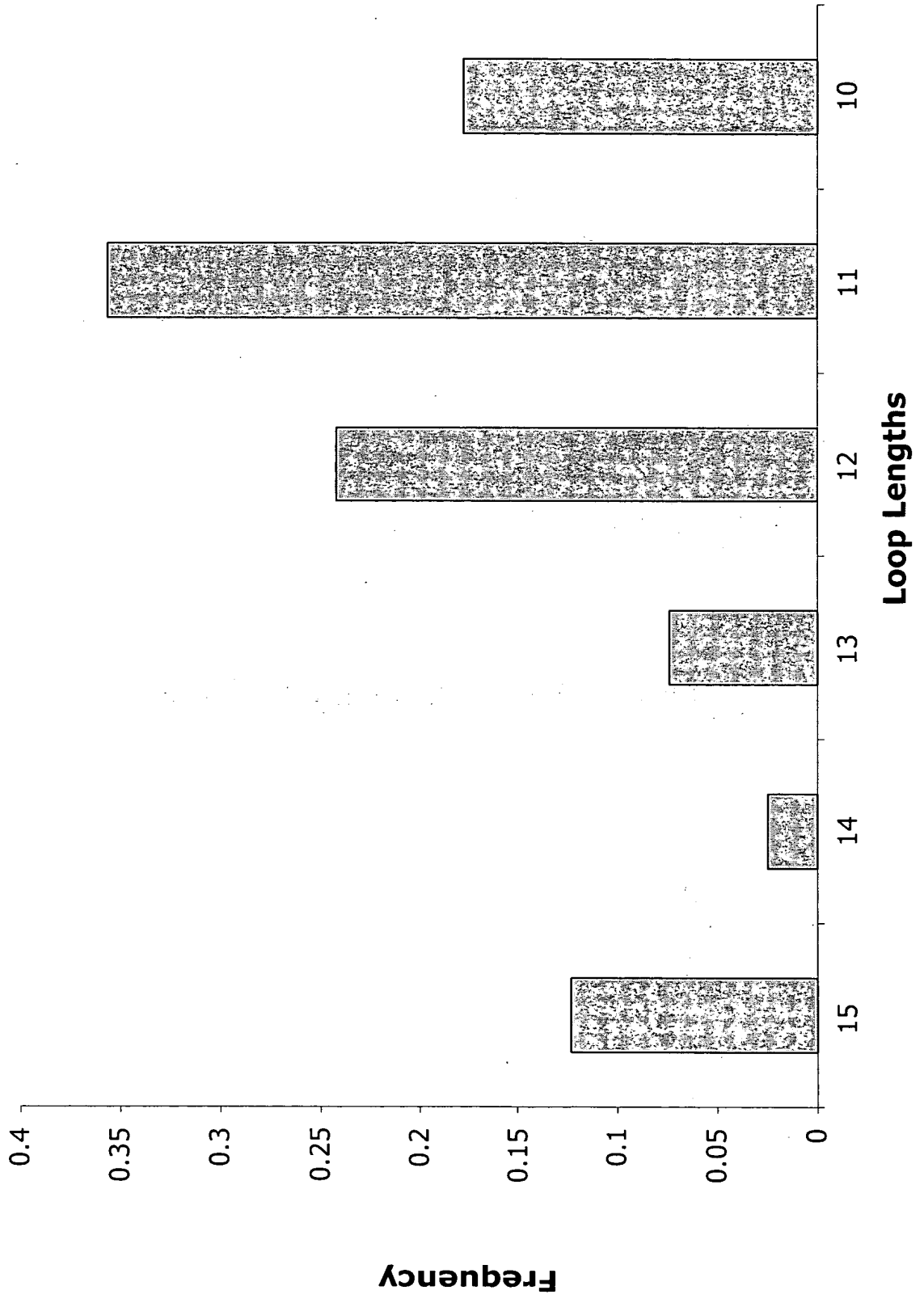


FIG. 47

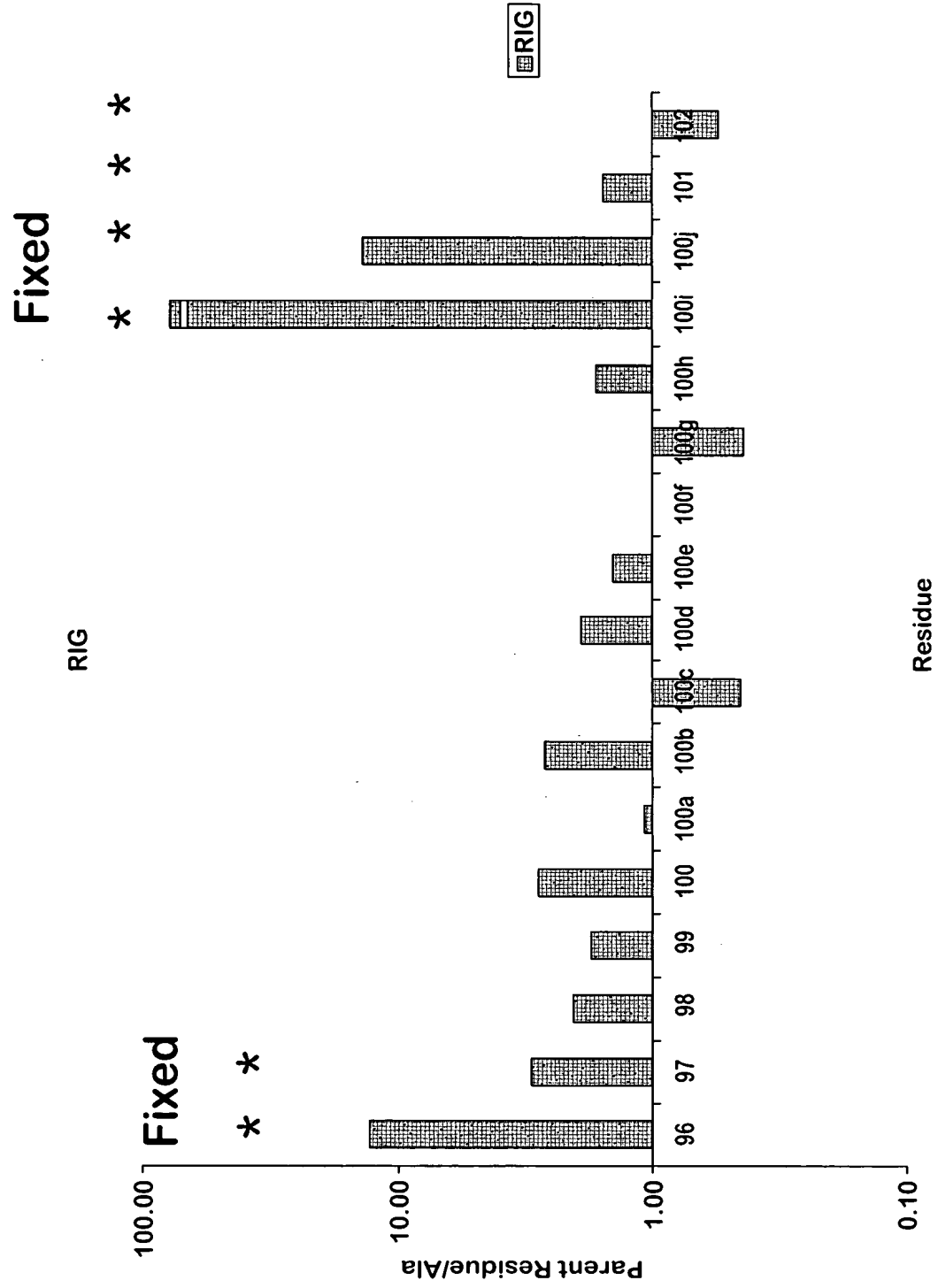


FIG.48

Residue	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H
98	3.36	0.33	0.33	0.33	0.33	0.33	0.33	4.36	2.69	0.33	-1.07	-0.26	0.33	0.33	0.33	0.33	0.33	0.33	4.76	0.33
99	5.21	0.33	0.33	0.33	0.33	0.33	0.33	-1.84	-0.78	0.33	-1.16	-1.55	0.33	0.72	0.33	0.33	0.33	0.33	0.33	0.33
100	0.41	-1.73	0.33	0.33	0.33	0.33	0.33	0.55	2.42	0.33	0.33	0.14	0.33	0.81	0.33	0.33	0.33	0.33	0.33	0.33
100a	-0.66	1.74	0.33	0.33	0.33	0.33	0.33	0.84	-2.18	0.33	2.97	-1.94	0.33	0.96	0.33	3.45	0.33	0.33	0.33	0.33
100b	0.51	0.47	0.33	0.33	0.33	0.33	0.33	1.82	0.95	0.33	0.33	-0.87	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33
100c	-1.85	0.77	0.33	0.33	0.33	0.33	0.33	-0.09	1.39	0.33	1.83	-0.64	0.15	0.33	0.33	3.69	0.33	0.33	1.94	0.33
100d	-1.69	-0.28	0.33	0.33	0.33	0.33	0.33	0.21	-1.99	0.33	3.57	0.81	0.33	1.30	0.33	0.33	0.33	0.33	0.33	0.33
100e	-1.58	-0.17	0.33	0.33	0.33	0.33	0.33	-2.40	1.87	0.33	0.33	2.95	0.38	4.95	0.33	0.33	0.33	0.33	0.33	0.33
100f	0.21	-0.06	0.33	0.33	0.33	0.33	0.33	-2.26	-1.83	0.33	2.47	-0.17	11.51	0.33	0.33	0.33	0.33	0.33	0.33	0.33
100g	4.30	0.46	0.33	0.33	0.33	0.33	0.33	-1.72	-0.66	0.33	0.33	-0.91	0.02	0.33	0.33	3.29	0.33	0.33	0.33	0.33
100h	-1.51	1.22	0.33	0.33	0.33	0.33	0.33	0.52	-1.87	0.33	0.79	2.44	0.33	1.54	0.33	0.33	0.33	0.33	0.33	0.33

no!q!y! %

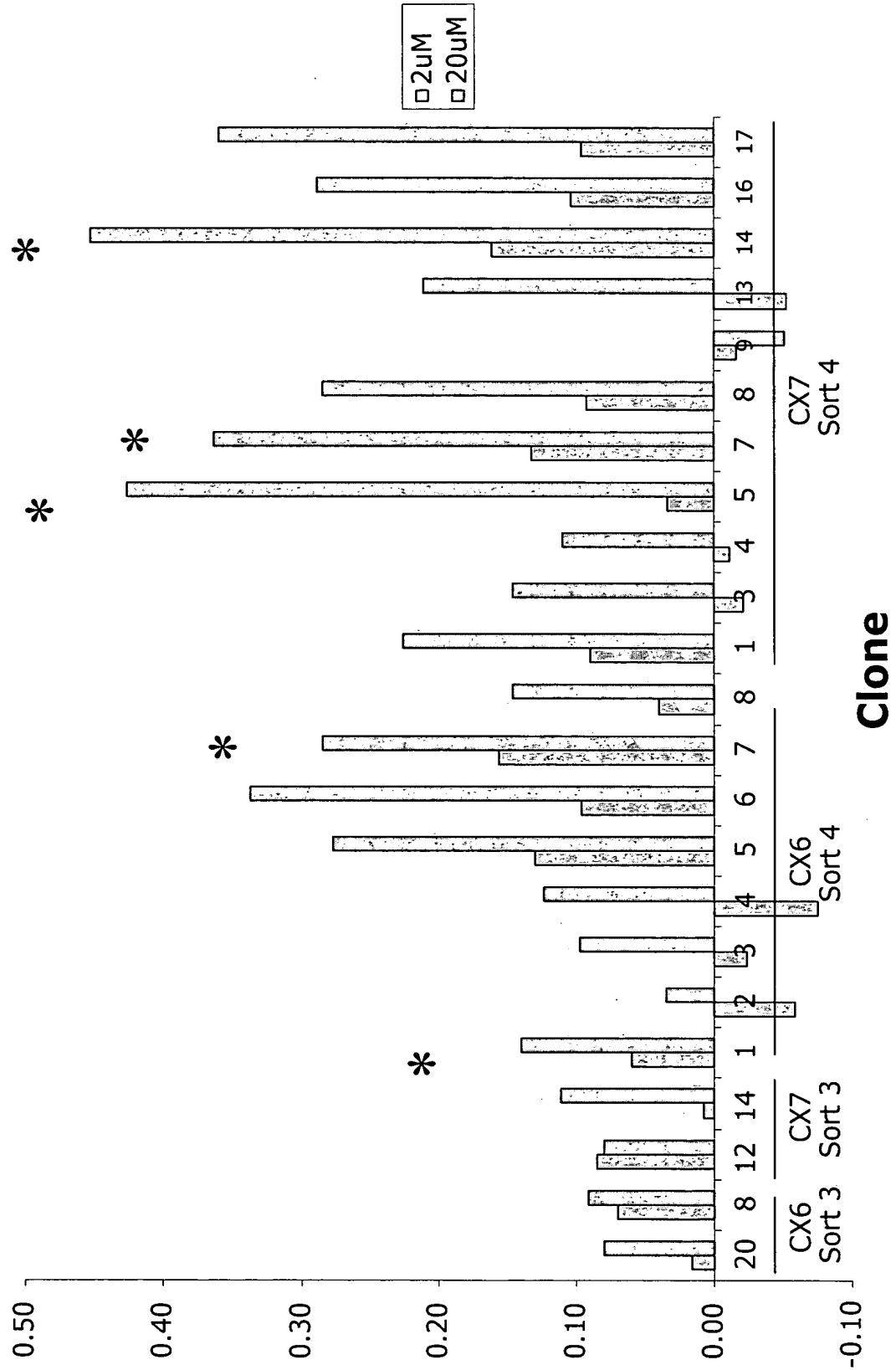


FIG. 50

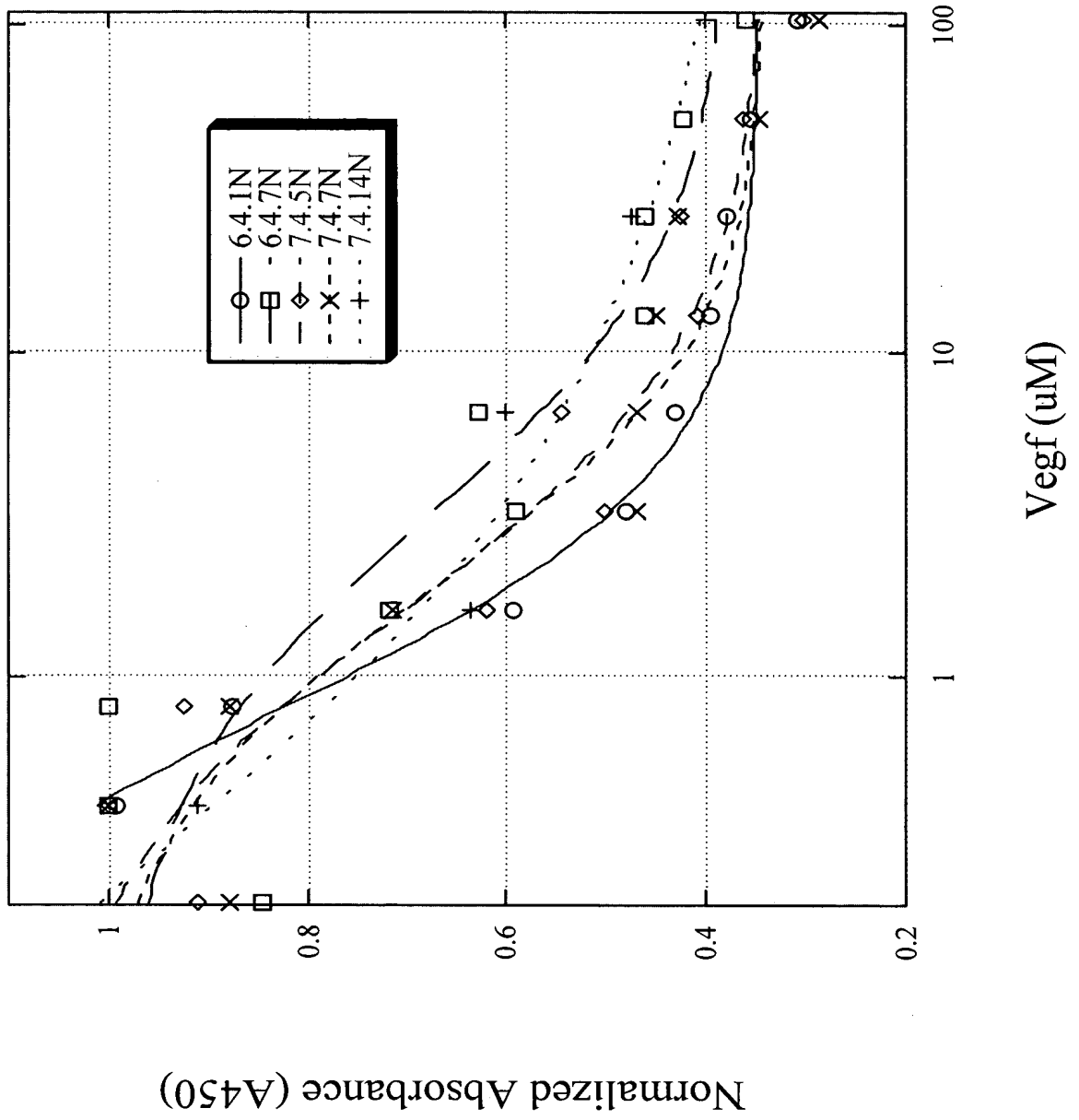




FIG. 51

FIG.52

Residue	C	A	V	L	I	P	F	Y	W	M	G	S	T	N	Q	D	E	K	R	H
37	1.2 #####	0.5	-0.7 #####	1.4	3.5	#####	0.0	#####	#####	#####	#####	1.2	#####	#####	#####	#####	1.2	#####	#####	#####
45	#####	1.0	-0.1	0.2 #####	#####	1.8	#####	#####	-1.2	1.2	1.3	#####	#####	#####	#####	#####	#####	#####	3.0	#####
47	#####	0.7	0.3	1.3 #####	#####	0.0	1.3	#####	-1.5	2.2	0.2	0.2	#####	#####	1.5	#####	#####	#####	-0.8	#####
91	#####	#####	#####	-0.7	1.6	#####	0.5	0.1	-1.5	#####	#####	0.2	4.3	1.6	#####	#####	#####	#####	-0.4	1.6

FIG. 53

